



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07K 5/023, A61K 38/06, 38/07	A1	(11) International Publication Number: WO 95/35308 (43) International Publication Date: 28 Décembre 1995 (28.12.95)
(21) International Application Number: PCT/US95/07617 (22) International Filing Date: 16 June 1995 (16.06.95) (30) Priority Data: 08/261,452 17 June 1994 (17.06.94) US 08/405,581 17 March 1995 (17.03.95) US 08/440,898 25 May 1995 (25.05.95) US (71) Applicant: VERTEX PHARMACEUTICALS INCORPORATED [US/US]; 40 Allston Street, Cambridge, MA 02139-4211 (US). (72) Inventors: BEMIS, Guy, W.; 256 Appleton Street, Arlington, MA 02174 (US). GOLEC, Julian, M., C.; 8 Manor Farm, Chapel Road, Ashbury, Swindon, Wiltshire SN6 8LS (GB). LAUFFER, David, J.; 254 Taylor Road, Stow, MA 01775 (US). MULLICAN, Michael, D.; 110 Parker Road, Needham, MA 02194 (US). MURCKO, Mark, A.; 520 Marshall Street, Holliston, MA 01746 (US). LIVINGSTON, David, J.; 20 Madison Avenue, Newtonville, MA 02160 (US). (74) Agents: HALEY, James, F., Jr. et al.; Fish & Neave, 1251 Avenue of the Americas, New York, NY 10020-1104 (US).		(81) Designated States: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TT, UA, UG, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG). Published <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
(54) Title: INHIBITORS OF INTERLEUKIN-1 β CONVERTING ENZYME		
(57) Abstract <p>The present invention relates to novel classes of compounds which are inhibitors of interleukin-1β converting enzyme. The ICE inhibitors of this invention are characterized by specific structural and physicochemical features. This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting ICE activity and consequently may be advantageously used as agents against interleukin-1 mediated diseases, including inflammatory diseases, autoimmune diseases and neurodegenerative diseases. This invention also relates to methods for inhibiting ICE activity and methods for treating interleukin-1 mediated diseases using the compounds and compositions of this invention.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AT	Austria	GB	United Kingdom	MR	Mauritania
AU	Australia	GE	Georgia	MW	Malawi
BB	Barbados	GN	Guinea	NE	Niger
BE	Belgium	GR	Greece	NL	Netherlands
BF	Burkina Faso	HU	Hungary	NO	Norway
BG	Bulgaria	IE	Ireland	NZ	New Zealand
BJ	Benin	IT	Italy	PL	Poland
BR	Brazil	JP	Japan	PT	Portugal
BY	Belarus	KE	Kenya	RO	Romania
CA	Canada	KG	Kyrgyzstan	RU	Russian Federation
CF	Central African Republic	KP	Democratic People's Republic of Korea	SD	Sudan
CG	Congo	KR	Republic of Korea	SE	Sweden
CH	Switzerland	KZ	Kazakhstan	SI	Slovenia
CI	Côte d'Ivoire	LI	Liechtenstein	SK	Slovakia
CM	Cameroon	LK	Sri Lanka	SN	Senegal
CN	China	LU	Luxembourg	TD	Chad
CS	Czechoslovakia	LV	Latvia	TG	Togo
CZ	Czech Republic	MC	Monaco	TJ	Tajikistan
DE	Germany	MD	Republic of Moldova	TT	Trinidad and Tobago
DK	Denmark	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	US	United States of America
FI	Finland	MN	Mongolia	UZ	Uzbekistan
FR	France			VN	Viet Nam
GA	Gabon				

INHIBITORS OF INTERLEUKIN-1 β CONVERTING ENZYME

TECHNICAL FIELD OF THE INVENTION

The present invention relates to novel
5 classes of compounds which are inhibitors of
interleukin-1 β converting enzyme ("ICE"). The ICE
inhibitors of this invention are characterized by
specific structural and physicochemical features. This
invention also relates to pharmaceutical compositions
10 comprising these compounds. The compounds and
pharmaceutical compositions of this invention are
particularly well suited for inhibiting ICE activity
and consequently, may be advantageously used as agents
against interleukin-1 ("IL-1") mediated diseases,
15 including inflammatory diseases, autoimmune diseases
and neurodegenerative diseases. This invention also
relates to methods for inhibiting ICE activity and
methods for treating interleukin-1 mediated diseases
using the compounds and compositions of this invention.

BACKGROUND OF THE INVENTION

Interleukin 1 ("IL-1") is a major pro-
inflammatory and immunoregulatory protein that
stimulates fibroblast differentiation and
proliferation, the production of prostaglandins,
25 collagenase and phospholipase by synovial cells and
chondrocytes, basophil and eosinophil degranulation and

- 2 -

neutrophil activation. Oppenheim, J.H. et al, Immunology Today, 7, pp. 45-56 (1986). As such, it is involved in the pathogenesis of chronic and acute inflammatory and autoimmune diseases. IL-1 is
5 predominantly produced by peripheral blood monocytes as part of the inflammatory response and exists in two distinct agonist forms, IL-1 α and IL-1 β . Mosely, B.S. et al., Proc. Nat. Acad. Sci., 84, pp. 4572-4576 (1987); Lonnemann, G. et al., Eur.J. Immunol., 19,
10 pp. 1531-1536 (1989).

IL-1 β is synthesized as a biologically inactive precursor, pIL-1 β . pIL-1 β lacks a conventional leader sequence and is not processed by a signal peptidase. March, C.J., Nature, 315,
15 pp. 641-647 (1985). Instead, pIL-1 β is cleaved by interleukin-1 β converting enzyme ("ICE") between Asp-116 and Ala-117 to produce the biologically active C-terminal fragment found in human serum and synovial fluid. Sleath, P.R., et al., J. Biol. Chem., 265,
20 pp. 14526-14528 (1992); A.D. Howard et al., J. Immunol., 147, pp. 2964-2969 (1991). Processing by ICE is also necessary for the transport of mature IL-1 β through the cell membrane.

ICE is a cysteine protease localized
25 primarily in monocytes. It converts precursor IL-1 β to the mature form. Black, R.A. et al., FEBS Lett., 247, pp. 386-390 (1989); Kostura, M.J. et al., Proc. Natl. Acad. Sci. USA, 86, pp. 5227-5231 (1989). ICE, or its homologues, also appears to be involved in the
30 regulation of cell death or apoptosis. Yuan, J. et al., Cell, 75, pp. 641-652 (1993); Miura, M. et al., Cell, 75, pp. 653-660 (1993); Nett-Fiordalisi, M.A. et al., J. Cell Biochem., 17B, p. 117 (1993). In particular, ICE or ICE homologues are thought to be
35 associated with the regulation of apoptosis in

- 3 -

neurogenerative diseases, such as Alzheimer's and Parkinson's disease. Marx, J. and M. Baringa, Science, 259, pp. 760-762 (1993); Gagliardini, V. et al., Science, 263, pp. 826-828 (1994).

5 ICE has been previously described as a heterodimer composed of two subunits, p20 and p10 (20kDa and 10kDa molecular weight, respectively). These subunits are derived from a 45kDa proenzyme (p45) by way of a p30 form, through an activation mechanism
10 that is autocatalytic. Thornberry, N.A. et al., Nature, 356, pp. 768-774 (1992). The ICE proenzyme has been divided into several functional domains: a prodomain (p14), a p22/20 subunit, a polypeptide linker and a p10 subunit. Thornberry et al., supra; Casano
15 et al., Genomics, 20, pp. 474-481 (1994).

Full length p45 has been characterized by its cDNA and amino acid sequences. PCT patent applications WO 91/15577 and WO 94/00154. The p20 and p10 cDNA and amino acid sequences are also known. Thornberry
20 et al., supra. Murine and rat ICE have also been sequenced and cloned. They have high amino acid and nucleic acid sequence homology to human ICE. Miller, D.K. et al., Ann. N.Y. Acad. Sci., 696, pp. 133-148 (1993); Molineaux, S.M. et al., Proc. Nat. Acad. Sci.,
25 90, pp. 1809-1813 (1993). Knowledge of the primary structure of ICE, however, does not allow prediction of its tertiary structure. Nor does it afford an understanding of the structural, conformational and chemical interactions of ICE and its substrate pIL-1 β
30 or other substrates or inhibitors.

ICE inhibitors represent a class of compounds useful for the control of inflammation or apoptosis or both. Peptide and peptidyl inhibitors of ICE have been described. PCT patent applications WO 91/15577; WO
35 93/05071; WO 93/09135; WO 93/14777 and WO 93/16710; and

- 4 -

European patent application 0 547 699. However, due to their peptidic nature, such inhibitors are typically characterized by undesirable pharmacologic properties, such as poor oral absorption, poor stability and rapid metabolism. Plattner, J.J. and D.W. Norbeck, in Drug Discovery Technologies, C.R. Clark and W.H. Moos, Eds. (Ellis Horwood, Chichester, England, 1990), pp. 92-126. This has hampered their development into effective drugs.

Accordingly, the need exists for compounds that can effectively inhibit the action of ICE, for use as agents for preventing and treating chronic and acute forms of IL-1 mediated diseases, including various cancers, as well as inflammatory, autoimmune or neurodegenerative diseases.

SUMMARY OF THE INVENTION

The present invention provides novel classes of compounds, and pharmaceutically acceptable derivatives thereof, that are useful as inhibitors of ICE. These compounds can be used alone or in combination with other therapeutic or prophylactic agents, such as antibiotics, immunomodulators or other anti-inflammatory agents, for the treatment or prophylaxis of diseases mediated by IL-1. According to a preferred embodiment, the compounds of this invention are capable of binding to the active site of ICE and inhibiting the activity of that enzyme.

It is a principal object of this invention to provide novel classes of inhibitors of ICE. These novel classes of ICE inhibitors are characterized by the following structural and physicochemical features:

a) a first and a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom

- 5 -

of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

5 b) a first and a second moderately hydrophobic moiety, said moieties each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2
10 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

 c) an electronegative moiety comprising one or more electronegative atoms, said
15 atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

It is also an object of this invention to provide a method for identification, design or
20 prediction of ICE inhibitors comprising the steps of:

 a) selecting a candidate compound of defined chemical structure comprising at least two hydrogen bonding moieties, at least two moderately hydrophobic moieties and one electronegative moiety
25 comprising one or more electronegative atoms attached either to the same atom or to adjacent atoms in the electronegative moiety;

 b) determining a low-energy conformation for binding of said compound to the active site of ICE;

30 c) evaluating the capability of said compound in said conformation to form at least two hydrogen bonds with the non-carbon backbone atoms of Arg-341 and Ser-339 of ICE;

 d) evaluating the capability of said
35 compound in said conformation to associate with at

- 6 -

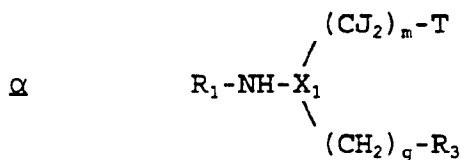
least two of the binding pockets of ICE selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket;

5 e) evaluating the capability of said compound in said conformation to interact with the P1 binding pocket of ICE; and

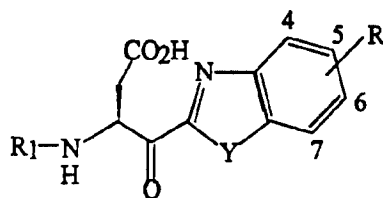
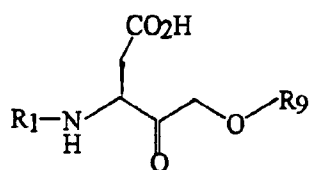
f) accepting or rejecting said candidate compound as an ICE inhibitor based on the determinations and evaluations carried out in the preceding steps.

It is a further object of this invention to provide novel classes of ICE inhibitors represented by formulas:

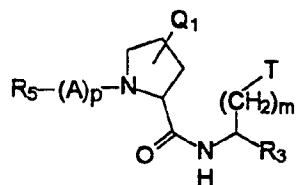
15



20

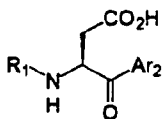
 β  π 

25

 γ 

, and

30

 δ 

- 7 -

ABBREVIATIONS AND DEFINITIONS

		<u>Abbreviations</u>	
		<u>Designation</u>	<u>Reagent or Fragment</u>
5		Ala	alanine
		Arg	arginine
		Asn	asparagine
		Asp	aspartic acid
		Cys	cysteine
10		Gln	glutamine
		Glu	glutamic acid
		Gly	glycine
		His	histidine
		Ile	isoleucine
15		Leu	leucine
		Lys	lysine
		Met	methionine
		Phe	phenylalanine
		Pro	proline
20		Ser	serine
		Thr	threonine
		Trp	tryptophan
		Tyr	tyrosine
		Val	valine.

Definitions

25 The following terms are employed herein:

 The term "active site" refers to any or all of the following sites in ICE: the substrate binding site, the site where an inhibitor binds and the site where the cleavage of substrate occurs. The active
30 site is characterized by at least amino acid residues: 173, 176, 177, 178, 179, 180, 236, 237, 238, 239, 244, 248, 283, 284, 285, 290, 338, 339, 340, 341, 342, 343,

- 8 -

344, 345, 348, 352, 381, 383, using the sequence and numbering according to Thornberry et al., supra.

5 The terms "P binding pocket", "S subsite", "S pocket", and the like, refer to binding subsites, or portions of the substrate binding site on the ICE molecule. The amino acid residues of the substrate are given designations according to their position relative to the scissile bond, i.e. the bond which is broken by the protease. The residues are designated P1, P2,
10 etc., for those extending toward the N-terminus of the substrate and P1', P2', etc., for those extending toward the C-terminus of the substrate. The portions of an inhibitor which correspond to the P or P' residues of the substrate are also labeled P1, P1',
15 etc., by analogy with the substrate. The binding subsites of the ICE molecule which receive the residues labeled P1, P1', etc., are designated S1, S1', etc., or may alternately be designated "the P1 binding pocket", "the P1' binding pocket", etc. [I. Schechter and A.
20 Berger, "On the Size of the Active Site in Proteases", Biochem. Biophys. Res. Commun., vol. 27, pp. 157-162 (1967).]

25 The terms "P2 binding pocket" or "S2 subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues Pro-290, Val-338 or Trp-340.

The terms "P3 binding pocket" or "S3 subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues Pro-177,
30 Arg-178, Thr-180, Arg-341 or Pro-343.

The terms "P4 binding pocket" or "S4 subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues His-342, Met-345, Val-348, Arg-352, Asp-381, Arg-383 or Trp-340.

- 9 -

The terms "P1 binding pocket" or "S1 subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues Arg-179, His-237, Gln-283, or Arg-341.

5 The terms "P' binding pocket" or "S' subsite" of the ICE active site are equivalent and are defined as the space surrounded by amino acid residues Phe-173, Ile-176, His-237, Gly-238, Ile-239, Cys-244 or His-248.

10 The term "hydrophobic" refers to a moiety which tends not to dissolve in water and is fat-soluble. Hydrophobic moieties include, but are not limited to, hydrocarbons, such as alkanes, alkenes, alkynes, cycloalkanes, cycloalkenes, cycloalkynes and aromatic compounds, such as aryls, certain saturated
15 and unsaturated heterocycles and moieties that are substantially similar to the side chains of hydrophobic natural and unnatural α -amino acids, including valine, leucine, isoleucine, methionine, phenylalanine, α -amino isobutyric acid, alloisoleucine, tyrosine, and
20 tryptophan.

 The term "moderately hydrophobic" refers to a hydrophobic moiety in which one or two carbon atoms have been replaced with more polar atoms, such as oxygen or nitrogen.

25 The term "heterocycle" or "heterocyclic" refers to a stable mono- or polycyclic compound which may optionally contain one or two double bonds or may optionally contain one or more aromatic rings. Each heterocycle consists of carbon atoms and from one to
30 four heteroatoms independently selected from a group including nitrogen, oxygen, and sulfur. As used herein, the terms "nitrogen heteroatoms" and "sulphur heteroatoms" include any oxidized form of nitrogen or sulfur and the quaternized form of any basic nitrogen.
35 Heterocycles defined above include, for example,

- 10 -

pyrimidinyl, tetrahydroquinolyl,
tetrahydroisoquinolyl, purinyl, pyrimidyl,
indolinyl, benzimidazolyl, imidazolyl, imidazolinoyl,
imidazolidinyl, quinolyl, isoquinolyl, indolyl,
5 pyridyl, pyrrolyl, pyrrolinyl, pyrazolyl, pyrazinyl,
quinoxolyl, piperidinyl, morpholinyl, thiamorpholinyl,
furyl, thienyl, triazolyl, thiazolyl, β -carbolinyl,
tetrazolyl, thiazolidinyl, benzofuranoyl,
thiamorpholinyl sulfone, benzoxazolyl, oxopiperidinyl,
10 oxopyrroldinyl, oxoazepinyl, azepinyl, isoxazolyl,
tetrahydropyranyl, tetrahydrofuranyl, thiadiazolyl,
benzodioxolyl, benzothienyl, tetrahydrothiophenyl and
sulfolanyl. Further heterocycles are described in A.R.
Katritzky and C.W. Rees, eds., Comprehensive
15 Heterocyclic Chemistry: The Structure, Reactions,
Synthesis and Use of Heterocyclic Compounds, Vol. 1-8,
Pergamon Press, NY (1984).

The term "cycloalkyl" refers to a mono- or
polycyclic group which contains 3 to 15 carbons and may
20 optionally contain one or two double bonds. Examples
include cyclohexyl, adamantyl and norbornyl.

The term "aryl" refers to a mono- or
polycyclic group which contains 6, 10, 12, or 14
carbons in which at least one ring is aromatic.
25 Examples include phenyl, naphthyl and biphenyl.

The term "heteroaromatic" refers to a mono-
or polycyclic group which contains 1 to 15 carbon atoms
and from 1 to 4 heteroatoms, each of which is selected
independently from a group including sulphur, nitrogen
30 and oxygen, and which additionally contains from 1 to 3
five or six membered rings, at least one of which is
aromatic.

The term "alpha-amino acid" (α -amino acid)
refers to both the naturally occurring amino acids and
35 other "non-protein" α -amino acids commonly utilized by

- 11 -

those in the peptide chemistry arts when preparing synthetic analogues of naturally occurring peptides, including D and L forms. The naturally occurring amino acids are glycine, alanine, valine, leucine, iso-

5 leucine, serine, methionine, threonine, phenylalanine, tyrosine, tryptophan, cysteine, proline, histidine, aspartic acid, asparagine, glutamic acid, glutamine, γ -carboxyglutamic acid, arginine, ornithine and lysine. Examples of "non-protein" alpha-amino acids include

10 hydroxylysine, homoserine, homotyrosine, homophenylalanine, citrulline, kynurenine, 4-amino-phenylalanine, 3-(2-naphthyl)-alanine, 3-(1-naphthyl)-alanine, methionine sulfone, t-butyl-alanine, t-butylglycine, 4-hydroxyphenylglycine, aminoalanine,

15 phenylglycine, vinylalanine, propargyl-glycine, 1,2,4-triazolo-3-alanine, 4,4,4-trifluoro-threonine, thyronine, 6-hydroxytryptophan, 5-hydroxytryptophan, 3-hydroxykynurenine, 3-aminotyrosine, trifluoromethyl-alanine, 2-thienylalanine, (2-(4-pyridyl)ethyl)-

20 cysteine, 3,4-dimethoxy-phenylalanine, 3-(2-thiazolyl)-alanine, ibotenic acid, 1-amino-1-cyclopentane-carboxylic acid, 1-amino-1-cyclohexanecarboxylic acid, quisqualic acid, 3-trifluoromethylphenylalanine, 4-trifluoro-methylphenylalanine, cyclohexylalanine,

25 cyclo-hexylglycine, thiohistidine, 3-methoxytyrosine, elastatinal, norleucine, norvaline, alloseleucine, homoarginine, thioproline, dehydroproline, hydroxyproline, isonipectotic acid, homoproline, cyclohexylglycine, α -amino-n-butyric acid, cyclohexylalanine,

30 aminophenylbutyric acid, phenylalanines substituted at the ortho, meta, or para position of the phenyl moiety with one or two of the following: a (C_1 - C_4) alkyl, a (C_1 - C_4) alkoxy, halogen or nitro groups or substituted with a methylenedioxy group; β -2- and 3-thienyl-

35 alanine, β -2- and 3-furanylalanine, β -2-, 3- and

- 12 -

4-pyridylalanine, β -(benzothienyl-2- and 3-yl)alanine, β -(1- and 2-naphthyl)alanine, O-alkylated derivatives of serine, threonine or tyrosine, S-alkylated cysteine, S-alkylated homocysteine, O-sulfate, O-phosphate and O-carboxylate esters of tyrosine, 3-sulfo-tyrosine, 3-carboxy-tyrosine, 3-phospho-tyrosine, 4-methane sulfonic acid ester of tyrosine, 4-methane phosphonic acid ester of tyrosine, 3,5-diiodotyrosine, 3-nitro-tyrosine, ϵ -alkyl lysine, and delta-alkyl ornithine.

Any of these α -amino acids may be substituted with a methyl group at the alpha position, a halogen at any aromatic residue on the α -amino side chain, or an appropriate protective group at the O, N, or S atoms of the side chain residues. Appropriate protective groups are disclosed in "Protective Groups In Organic Synthesis," T.W. Greene and P.G.M. Wuts, J. Wiley & Sons, NY, NY, 1991.

The term " α -amino acid side chain residue" refers to a chemical moiety which is attached to the α -carbon of an alpha-amino acid.

The term "bioisosteric replacement for $-\text{CO}_2\text{H}$ " refers to group which may substitute for a carboxylic acid group in bioactive molecules. Examples of such groups are disclosed in Christopher A. Lipinski, "Bioisosteres in Drug Design" Annual Reports In Medical Chemistry, 21, pp. 286-88 (1986), and in C.W. Thornber, "Isosterism and Molecular Modification in Drug Design" Chemical Society Reviews, pp. 563-580 (1979).

The term "association" is used in reference to a condition of proximity between an inhibitor or portions thereof to an ICE molecule or portions thereof wherein the juxtaposition is energetically favored by electrostatic or van der Waals interactions.

The term "hydrogen bond" refers to a favorable interaction that occurs whenever a suitable

- 13 -

donor atom, X, bearing a proton, H, and a suitable acceptor atom, Y, have a separation of between 2.5Å and 3.5Å and where the angle X-H - - - Y is greater than 90 degrees. Suitable donor and acceptor atoms are well understood in medicinal chemistry (G.C. Pimentel and A.L. McClellan, The Hydrogen Bond, Freeman, San Francisco, 1960; R. Taylor and O. Kennard, "Hydrogen Bond Geometry in Organic Crystals", Accounts of Chemical Research, 17, pp. 320-326 (1984)).

The term "salt bridge" refers to the non-covalent attractive interaction between a positively charged moiety (P) and a negatively charged moiety (N) when the distance between the centers of mass of P and N is between 2 and 6 Angstroms. In calculating the center of mass, atoms which may contain a formal charge and atoms immediately adjacent to these are included. For example, a salt bridge may be formed between the positively charged guanidinium side chain of an arginine residue and the negative charged carboxylate side chain of a glutamate residue. Salt bridges are well understood in medicinal chemistry (L. Stryer, Biochemistry, Freeman, San Francisco, (1975); K.A. Dill, "Dominant Forces in Protein Folding", Biochemistry, 29, No. 31, pp. 7133-7155, (1990)).

The term "center of mass" refers to a point in three-dimensional space which represents a weighted average position of the masses that make up an object.

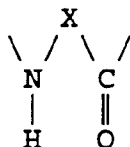
The terms "backbone chain" and "backbone" refer to the portion of a polypeptide which comprises the repeating unit -CO-CH-NH-.

The term "scaffold" refers to a structural building block which forms the basis of an ICE inhibitor according to this invention. Various moieties and functional groups are intended to be appended to the scaffold. The scaffolds of this

- 14 -

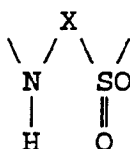
invention are thus depicted having open valences.
 Various scaffolds of ICE inhibitors according to this
 invention include the portions:

5



or

10



15 In those scaffolds, the NH and CO or SO₂ moieties
 represent a first and a second hydrogen bonding moiety,
 said moieties each being capable of forming a hydrogen
 bond with a backbone atom of ICE, said backbone atom
 being selected from the group consisting of the
 20 carbonyl oxygen of Arg-341, the amide -NH- of Arg-341,
 the carbonyl oxygen of Ser-339 and the amide -NH- of
 Ser-339.

The term "substitute" refers to the
 replacement of a hydrogen atom in a compound with a
 25 substituent group. In the present invention, those
 hydrogen atoms which form a part of a hydrogen bonding
 moiety which is capable of forming a hydrogen bond with
 the carbonyl oxygen of Arg-341 of ICE or the carbonyl
 oxygen of Ser-339 of ICE are excluded from
 30 substitution. These excluded hydrogen atoms include
 those which comprise an -NH- group which is alpha to a
 Z or a -CO- group and are depicted as -NH- rather than
 an X group or some other designation in the following
 diagrams: (a) through (t), (v) through (y), and (I)
 35 through (VIID).

- 15 -

The term "straight chain" refers to a contiguous unbranching string of covalently bound members, i.e. atoms, which form a portion of a ring. The straight chain and the ring of which it forms a part may be substituted, but these substituents are not a part of the straight chain.

The term " K_i " refers to a numerical measure of the effectiveness of a compound in inhibiting the activity of a target enzyme such as ICE. Lower values of K_i reflect higher effectiveness. The K_i value is a derived by fitting experimentally determined rate data to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

The term "minimize" refers to the systematic altering of the atomic geometry of a molecule or molecular complex so that any further minor perturbation of the atomic geometry would cause the total energy of the system as measured by a molecular mechanics force-field to increase. Minimization and molecular mechanics force-fields are well understood in computational chemistry [U. Burkert and N.L. Allinger, Molecular Mechanics, ACS Monograph 177, American Chemical Society, Washington, D.C. 1982 pages 59-78].

The term "strain energy" is used in this application to refer to the difference between the free conformation energy of a compound and the bound conformation energy of that compound when bound to ICE. The strain energy can be determined by the following steps: Evaluate the energy of the molecule when it has the conformation necessary for binding to ICE. Then minimize and reevaluate the energy -- this is the free conformation energy. The strain energy for binding of a potential inhibitor to ICE is the difference between the free conformation energy and the bound conformation energy. In a preferred embodiment, the strain energy

- 16 -

of an inhibitor of the present invention is less than about 10 kcal/mol.

The term "patient" as used in this application refers to any mammal, especially humans.

5 The term "pharmaceutically effective amount" refers to an amount effective in treating or ameliorating an IL-1 mediated disease in a patient. The term "prophylactically effective amount" refers to an amount effective in preventing or substantially
10 lessening IL-1 mediated disease in a patient.

 The term "pharmaceutically acceptable carrier or adjuvant" refers to a non-toxic carrier or adjuvant that may be administered to a patient, together with a compound of this invention, and which does not destroy
15 the pharmacological activity thereof.

 The term "pharmaceutically acceptable derivative" means any pharmaceutically acceptable salt, ester, or salt of such ester, of a compound of this invention or any other compound which, upon
20 administration to a recipient, is capable of providing (directly or indirectly) a compound of this invention or an anti-ICE active metabolite or residue thereof.

 Pharmaceutically acceptable salts of the compounds of this invention include, for example, those
25 derived from pharmaceutically acceptable inorganic and organic acids and bases. Examples of suitable acids include hydrochloric, hydrobromic, sulfuric, nitric, perchloric, fumaric, maleic, phosphoric, glycolic, lactic, salicylic, succinic, toluene-p-sulfonic,
30 tartaric, acetic, citric, methanesulfonic, formic, benzoic, malonic, naphthalene-2-sulfonic and benzenesulfonic acids. Other acids, such as oxalic, while not in themselves pharmaceutically acceptable, may be employed in the preparation of salts useful as
35 intermediates in obtaining the compounds of the

- 17 -

invention and their pharmaceutically acceptable acid addition salts. Salts derived from appropriate bases include alkali metal (e.g., sodium), alkaline earth metal (e.g., magnesium), ammonium and N-(C₁₋₄ alkyl)₄⁺ salts.

5 This invention also envisions the "quaternization" of any basic nitrogen-containing groups of the compounds disclosed herein. The basic nitrogen can be quaternized with any agents known to those of ordinary skill in the art including, for example, lower alkyl halides, such as methyl, ethyl, propyl and butyl chloride, bromides and iodides; dialkyl sulfates including dimethyl, diethyl, dibutyl and diamyl sulfates; long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides; and aralkyl halides including benzyl and phenethyl bromides. Water or oil-soluble or dispersible products may be obtained by such quaternization.

20 The ICE inhibitors of this invention may contain one or more "asymmetric" carbon atoms and thus may occur as racemates and racemic mixtures, single enantiomers, diastereomeric mixtures and individual diastereomers. All such isomeric forms of these compounds are expressly included in the present invention. Each stereogenic carbon may be of the R or S configuration. Although specific compounds and scaffolds exemplified in this application may be depicted in a particular stereochemical configuration, compounds and scaffolds having either the opposite stereochemistry at any given chiral center or mixtures thereof are also envisioned.

30 The ICE inhibitors of this invention may comprise ring structures which may optionally be substituted at carbon, nitrogen or other atoms by

35

- 18 -

various substituents. Such ring structures may be singly or multiply substituted. Preferably, the ring structures contain between 0 and 3 substituents. When multiply substituted, each substituent may be picked independently of any other substituent as long as the combination of substituents results in the formation of a stable compound.

Combinations of substituents and variables envisioned by this invention are only those that result in the formation of stable compounds. The term "stable", as used herein, refers to compounds which possess stability sufficient to allow manufacture and administration to a mammal by methods known in the art. Typically, such compounds are stable at a temperature of 40°C or less, in the absence of moisture or other chemically reactive conditions, for at least a week.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth.

We have discovered that compounds possessing the following novel combination of features are surprisingly effective ICE inhibitors:

a) a first and a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

b) a first and a second moderately hydrophobic moiety, said moieties each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket

- 19 -

being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

5 c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

10 Preferably, any moderately hydrophobic moiety associating with the P2 binding pocket of ICE does so in such a way that:

a) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 7.1Å and about 12.5Å;

b) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 6.0Å and about 12Å; and

c) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 3.7Å and about 9.5Å.

25 Preferably, any moderately hydrophobic moiety associating with the P3 binding pocket of ICE does so in such a way that:

a) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 3.9Å and about 9.5Å;

b) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 5.4Å and about 11Å; and

- 20 -

c) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 7.0Å and about 13Å.

5 Preferably, any moderately hydrophobic moiety associating with the P4 binding pocket of ICE does so in such a way that:

a) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 4.5Å and about 7.5Å;

b) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 5.5Å and about 8.5Å; and

c) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 8Å and about 11Å.

20 Preferably, any moderately hydrophobic moiety associating with the P' binding pocket of ICE does so in such a way that:

a) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 11Å and about 16Å;

b) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the amide nitrogen of Arg-341 of ICE is between about 10Å and about 15Å; and

30 c) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 8Å and about 12Å.

- 21 -

More preferably, all of the above associative conditions are met in the compounds of this invention.

The practitioner skilled in the art will appreciate that there are a number of means to design the inhibitors of the present invention. These same means may be used to select a candidate compound for screening as an ICE inhibitor. This design or selection may begin with selection of the various moieties which fill binding pockets.

There are a number of ways to select moieties to fill individual binding pockets. These include visual inspection of a physical model or computer model of the active site and manual docking of models of selected moieties into various binding pockets.

Modeling software that is well known and available in the art may be used. These include QUANTA [Molecular Simulations, Inc., Burlington, MA, 1992], SYBYL [Molecular Modeling Software, Tripos Associates, Inc., St. Louis, MO, 1992], AMBER [S.J. Weiner, P.A. Kollman, D.A. Case, U.C. Singh, C. Ghio, G. Alagona, and P. Weiner, J. Am. Chem. Soc., vol. 106, pp. 765-784 (1984)], or CHARMM [B.R. Brooks, R.E. Bruccoleri, B.D. Olafson, D.J. States, S Swaminathan, and M. Karplus, J. Comp. Chem. vol. 4, pp. 187-217 (1983)]. This modelling step may be followed by energy minimization with standard molecular mechanics forcefields such as CHARMM and AMBER. In addition, there are a number of more specialized computer programs to assist in the process of selecting the binding moieties of this invention. These include:

1. GRID (Goodford, P.J. A Computational Procedure for Determining Energetically Favorable Binding Sites on Biologically Important Macromolecules. J. Med. Chem., 28, pp. 849-857 (1985)). GRID is available from Oxford University, Oxford, UK.

- 22 -

2. MCSS (Miranker, A.; Karplus, M. Functionality Maps of Binding Sites: A Multiple Copy Simultaneous Search Method. Proteins: Structure, Function and Genetics, 11, pp. 29-34 (1991)). MCSS is available from Molecular Simulations, Burlington, MA.
3. AUTODOCK (Goodsell, D.S.; Olsen, A.J. Automated Docking of Substrates to Proteins by Simulated Annealing. PROTEINS: Structure, Function and Genetics, 8, pp. 195-202 (1990)). AUTODOCK is available from the Scripps Research Institute, La Jolla, CA.
4. DOCK (Kuntz, I.D.; Blaney, J.M.; Oatley, S.J.; Langridge, R.; Ferrin, T.E. A Geometric Approach to Macromolecule-Ligand Interactions. J. Mol. Biol., 161, pp. 269-288 (1982)). DOCK is available from the University of California, San Francisco, CA.
- Once suitable binding moieties have been selected, they can be assembled into a single inhibitor. This assembly may be accomplished by connecting the various moieties to a central scaffold. The assembly process may, for example, be done by visual inspection followed by manual model building, again using software such as Quanta or Sybyl. A number of other programs may also be used to help select ways to connect the various moieties. These include:
1. CAVEAT (Bartlett, P.A.; Shea, G.T.; Telfer, S.J.; Waterman, S. CAVEAT: A Program to Facilitate the Structure-Derived Design of Biologically Active Molecules. In "Molecular Recognition in Chemical and Biological Problems," Special Pub., Royal Chem. Soc., 78, pp. 182-196 (1989)). CAVEAT is available from the University of California, Berkeley, CA.
2. 3D Database systems such as MACCS-3D (MDL Information Systems, San Leandro, CA). This area has been recently reviewed by Martin (Martin, Y.C. 3D Database Searching in Drug Design. J. Med. Chem., 35, pp. 2145-2154 (1992)).

- 23 -

3. HOOK (available from Molecular Simulations, Burlington, MA).

In addition to the above computer assisted modeling of inhibitor compounds, the inhibitors of this invention may be constructed "de novo" using either an empty active site or optionally including some portions of a known inhibitor. Such methods are well known in the art. They include, for example:

1. LUDI (Bohm, H.J. The Computer Program LUDI: A New Method for the De Novo Design of Enzyme Inhibitors. J. Comp. Aid. Molec. Design., 6, 61-78 (1992)). LUDI is available from Biosym Technologies, San Diego, CA.

2. LEGEND (Nishibata, Y., Itai, A., Tetrahedron, 47, 8985 (1991)). LEGEND is available from Molecular Simulations, Burlington, MA.

3. LeapFrog (available from Tripos associates, St. Louis, MO).

A number of techniques commonly used for modeling drugs may be employed (For a review, see: Cohen, N.C.; Blaney, J.M.; Humblet, C.; Gund, P.; Barry, D.C., "Molecular Modeling Software and Methods for Medicinal Chemistry", J. Med. Chem., 33, pp. 883-894 (1990)). There are likewise a number of examples in the chemical literature of techniques that can be applied to specific drug design projects. For a review, see: Navia, M.A. and Murcko, M.A., "The Use of Structural Information in Drug Design", Current Opinions in Structural Biology, 2, pp. 202-210 (1992). Some examples of these specific applications include: Baldwin, J.J. et al., "Thienothiopyran-2-sulfonamides: Novel Topically Active Carbonic Anhydrase Inhibitors for the Treatment of Glaucoma", J. Med. Chem., 32, pp. 2510-2513 (1989); Appelt, K. et al., "Design of Enzyme Inhibitors Using Iterative Protein Crystallographic Analysis", J. Med. Chem., 34, pp. 1925-1934 (1991); and

- 24 -

Ealick, S.E. et al., "Application of Crystallographic and Modeling Methods in the Design of Purine Nucleotide Phosphorylase Inhibitors" Proc. Nat. Acad. Sci. USA, 88, pp. 11540-11544 (1991).

5 Using the novel combination of steps of the present invention, the skilled artisan can advantageously avoid time consuming and expensive experimentation to determine enzymatic inhibition activity of particular compounds. The method also is
10 useful to facilitate rational design of ICE inhibitors and therapeutic and prophylactic agents against IL-1-mediated diseases. Accordingly, the present invention relates to such inhibitors.

 A variety of conventional techniques may be
15 used to carry out each of the above evaluations as well as the evaluations necessary in screening a candidate compound for ICE inhibiting activity. Generally, these techniques involve determining the location and binding proximity of a given moiety, the occupied space of a
20 bound inhibitor, the deformation energy of binding of a given compound and electrostatic interaction energies. Examples of conventional techniques useful in the above evaluations include: quantum mechanics, molecular mechanics, molecular dynamics, Monte Carlo sampling,
25 systematic searches and distance geometry methods (G.R. Marshall, Ann. Ref. Pharmacol. Toxicol., 27, p. 193 (1987)). Specific computer software has been developed for use in carrying out these methods. Examples of programs designed for such uses include: Gaussian 92,
30 revision E.2 (M.J. Frisch, Gaussian, Inc., Pittsburgh, PA ©1993); AMBER, version 4.0 (P.A. Kollman, University of California at San Francisco, ©1993); QUANTA/CHARMM [Molecular Simulations, Inc., Burlington, MA ©1992]; and Insight II/Discover (Biosym Technologies Inc., San
35 Diego, CA ©1992). These programs may be implemented,

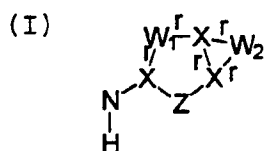
- 25 -

for instance, using a Silicon Graphics Indigo 2 workstation or IBM RISC/6000 workstation model 550. Other hardware systems and software packages will be known and of evident applicability to those skilled in the art.

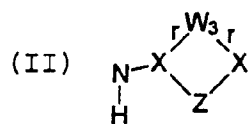
Different classes of active ICE inhibitors, according to this invention, may interact in similar ways with the various binding pockets of the ICE active site. The spatial arrangement of these important groups is often referred to as a pharmacophore. The concept of the pharmacophore has been well described in the literature (D. Mayer, C.B. Naylor, I. Motoc, and G.R. Marshall, J. Comp. Aided Molec. Design vol. 1, pp. 3-16 (1987); A. Hopfinger and B.J. Burke, in Concepts and Applications of Molecular Similarity, M.A. Johnson and G.M. Maggiora, ed., Wiley (1990)).

Different classes of ICE inhibitors of this invention may also use different scaffolds or core structures, but all of these cores will allow the necessary moieties to be placed in the active site such that the specific interactions necessary for binding may be obtained. These compounds are best defined in terms of their ability to match the pharmacophore, i.e., their structural identity relative to the shape and properties of the active site of ICE.

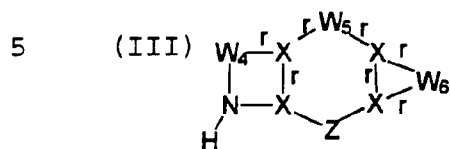
The ICE inhibitors of one embodiment of this invention comprise a first and a second hydrogen bonding moiety, a first and a second moderately hydrophobic moiety, and an electronegative moiety which comprise or are covalently bound to one of the following scaffolds:



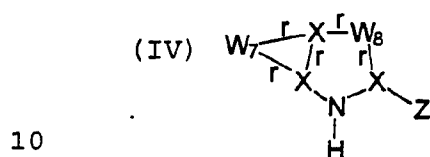
- 26 -



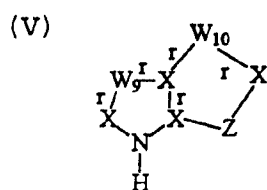
;



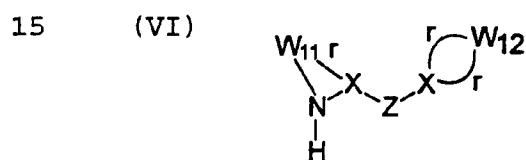
;



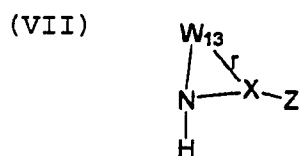
;



;



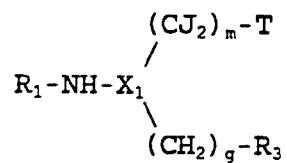
; and



20

The ICE inhibitors of another embodiment (A) of this invention are those of formula α :

25

 α 

- 27 -

wherein:

X_1 is CH or N;

g is 0 or 1;

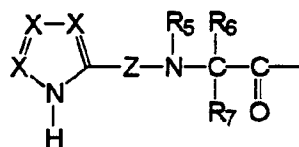
each J is independently selected from the group
 5 consisting of -H, -OH, and -F, provided that when a
 first and second J are bound to a C and said first J is
 -OH, said second J is -H;

m is 0, 1, or 2;

T is - Ar_3 , -OH, - CF_3 , -CO-CO₂H, -CO₂H or any
 10 bioisosteric replacement for -CO₂H;

R_1 is selected from the group consisting of the
 following formulae, in which any ring may optionally be
 singly or multiply substituted at any carbon by Q_1 , at
 any nitrogen by R_5 , or at any atom by =O, -OH, -CO₂H, or
 15 halogen, and in which any saturated ring may optionally
 be unsaturated at one or two bonds:

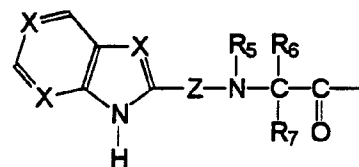
(a)



;

20

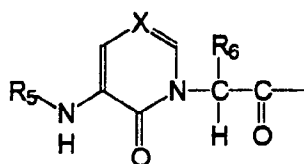
(b)



;

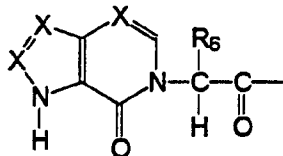
25

(c)

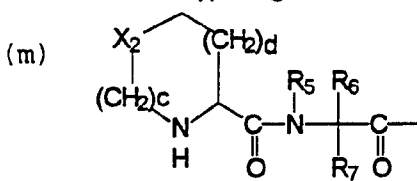
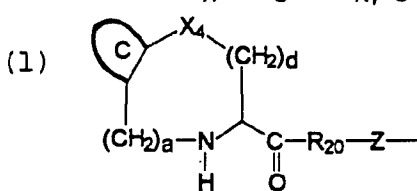
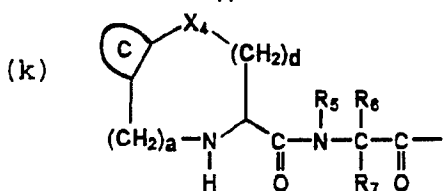
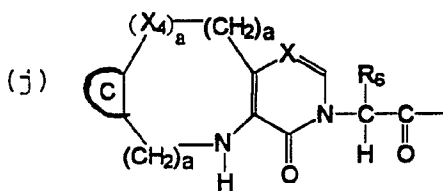
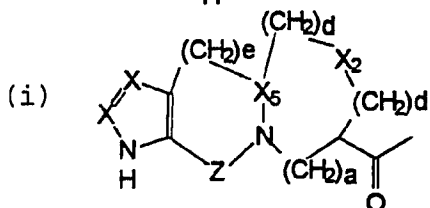
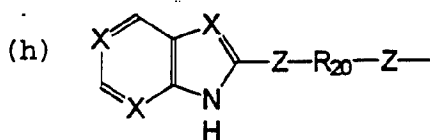
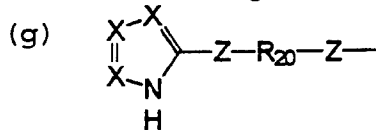
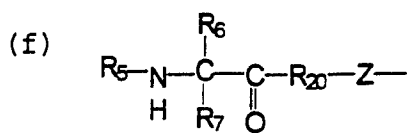
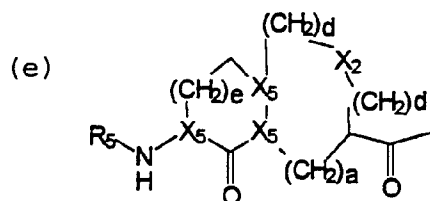


;

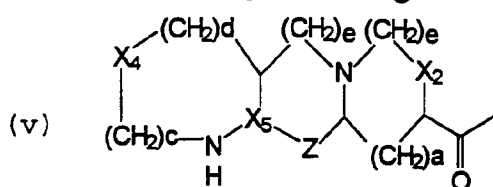
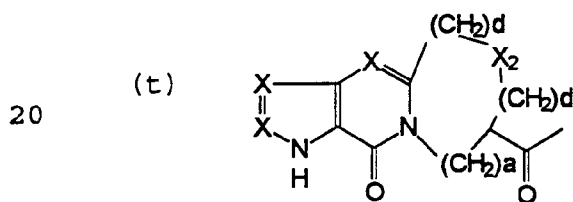
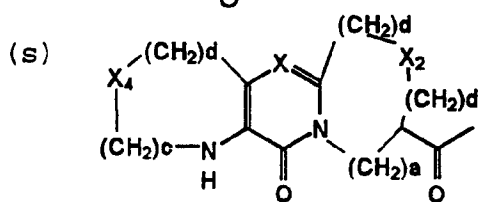
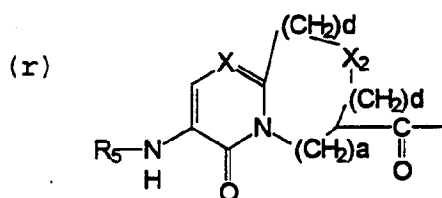
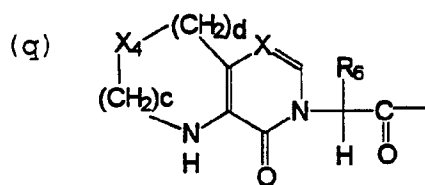
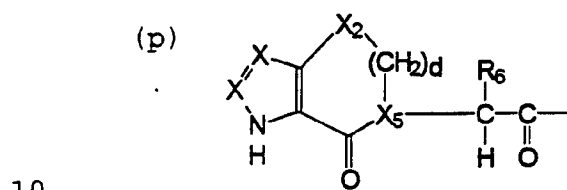
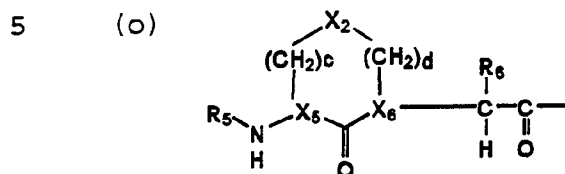
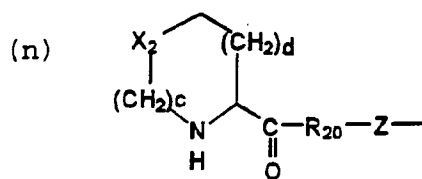
(d)



;

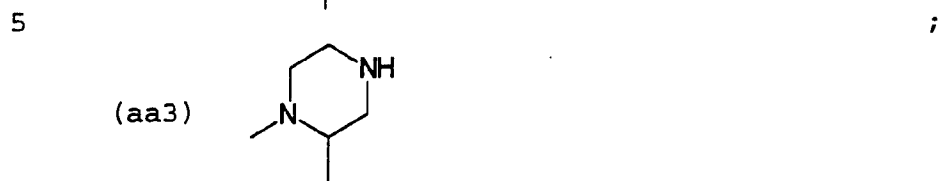


- 29 -



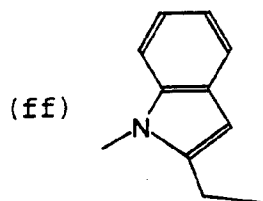
- 30 -

R₂₀ is selected from the group consisting of:

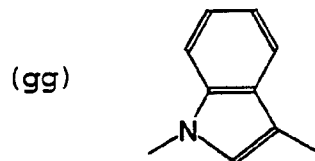


20

- 31 -

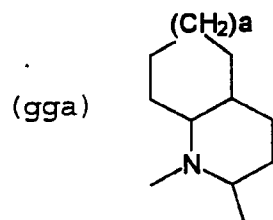


;

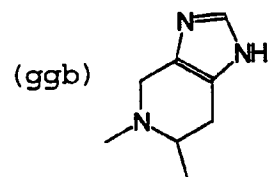


;

5

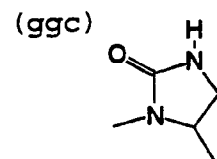


;



; and

10



;

15

wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

20

R_3 is

-CN,

-CH=CH- R_9 ,

-CH=N-O- R_9 ,

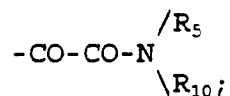
-(CH₂)₁₋₃-T₁- R_9 ,

-CJ₂- R_9 ,

25

-CO- R_{13} , or

- 32 -



each R_4 is independently selected from the group
 5 consisting of:

- H,
- Ar₁,
- R₉,
- T₁-R₉, and
- 10 - (CH₂)_{1,2,3}-T₁-R₉,

each T₁ is independently selected from the group
 consisting of:

- CH=CH-,
- O-,
- 15 -S-,
- SO-,
- SO₂-,
- NR₁₀-,
- NR₁₀-CO-,
- 20 -CO-,
- O-CO-,
- CO-O-,
- CO-NR₁₀-,
- O-CO-NR₁₀-,
- 25 -NR₁₀-CO-O-,
- NR₁₀-CO-NR₁₀-,
- SO₂-NR₁₀-,
- NR₁₀-SO₂-, and
- NR₁₀-SO₂-NR₁₀-,

30 each R₅ is independently selected from the group
 consisting of:

- H,
- Ar₁,

- 33 -

- CO-Ar₁,
 -SO₂-Ar₁,
 -R₉,
 -CO-R₉,
 5 -CO-O-R₉,
 -SO₂-R₉,
 /Ar₁
 -CO-N
 \R₁₀,
 10 /Ar₁
 -SO₂-N
 \R₁₀,
 /R₉
 -CO-N
 15 \R₁₀, and
 /R₉
 -SO₂-N
 \R₁₀,

- 20 R₆ and R₇ taken together form a saturated 4-8
 member carbocyclic ring or heterocyclic ring containing
 -O-, -S-, or -NH-, or
 R₇ is -H and R₆ is
 -H
 -Ar₁,
 25 -R₉, or
 -(CH₂)_{1,2,3}-T₁-R₉;

- 30 each R₉ is a C₁₋₆ straight or branched alkyl group
 optionally singly or multiply substituted by -OH, -F,
 or =O and optionally substituted with one or two Ar₁
 groups;

each R₁₀ is independently selected from the group
 consisting of -H or a C₁₋₆ straight or branched alkyl
 group;

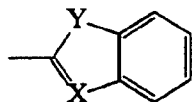
- 34 -

each R_{13} is independently selected from the group consisting of $-Ar_2$ and $-R_4$;

each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains
 5 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a
 10 heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from $-O-$, $-S-$, $-SO-$, $-SO_2-$, $=N-$, and $-NH-$, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or
 15 more aromatic rings, and said cyclic group optionally being singly or multiply substituted by $=O$, $-OH$, perfluoro C_{1-3} alkyl, or $-Q_1$;

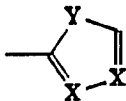
each Ar_2 is independently selected from the
 20 following group, in which any ring may optionally be substituted by $-Q_1$:

(hh)



;

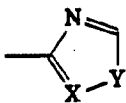
(ii)



;

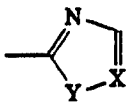
25

(jj)



; and

(kk)



;

30

- 35 -

Ar₃ is a cyclic group selected from the set consisting of a phenyl ring, a 5-membered heteroaromatic ring, and a 6-membered heteroaromatic ring, said heteroaromatic rings comprising 1-3 heteroatom groups selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said cyclic group optionally being singly or multiply substituted with =O, -OH, halogen, perfluoro C₁₋₃ alkyl, or -CO₂H;

each Q₁ is independently selected from the group consisting of:

-Ar₁
 -R₉,
 -T₁-R₉, and
 -(CH₂)_{1,2,3}-T₁-R₉,

provided that when -Ar₁ is substituted with a Q₁ group which comprises one or more additional -Ar₁ groups, said additional -Ar₁ groups are not substituted with Q₁;

each X is independently selected from the group consisting of =N-, and =CH-;

each X₂ is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂;
 each X₃ is independently selected from the group consisting of -CH₂-, -S-, -SO-, and -SO₂-;

each X₄ is independently selected from the group consisting of -CH₂- and -NH-;

each X₅ is independently selected from the group consisting of -CH- and -N-;

- 36 -

X_6 is CH or N, provided that when X_6 is N in the R_1 group labeled (o) and X_5 is CH and X_2 is CH_2 the ring of the R_1 group labeled (o) must be substituted by Q_1 or benzofused;

5 each Y is independently selected from the group consisting of -O- and -S-;

each Z is independently CO or SO_2 ,

each a is independently 0 or 1,

each c is independently 1 or 2,

10 each d is independently 0, 1, or 2, and

each e is independently 0, 1, 2, or 3.

The ICE inhibitors of another embodiment (B) of this invention are those of formula α :



20 wherein:

X_1 is -CH;

g is 0 or 1;

25 each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

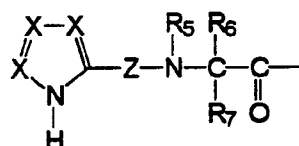
- 37 -

m is 0, 1, or 2;

T is -OH, -CO-CO₂H, -CO₂H or any bioisosteric replacement for -CO₂H;

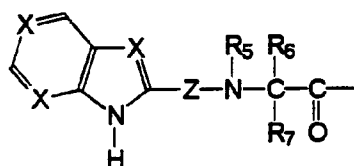
R₁ is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q₁, at any nitrogen by R₅, or at any atom by =O, -OH, -CO₂H, or halogen, any saturated ring may optionally be unsaturated at one or two bonds; and wherein R₁ (e) and R₁ (y) are optionally benzofused;

(a)



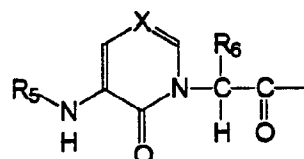
;

(b)



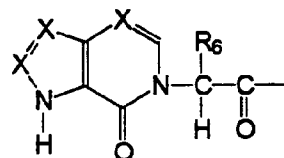
;

(c)



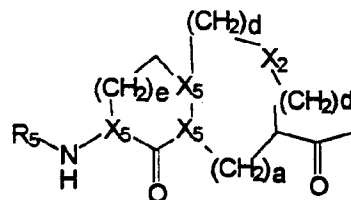
;

(d)

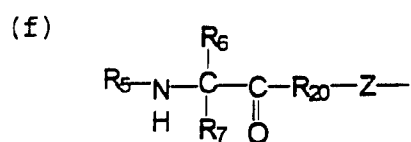


;

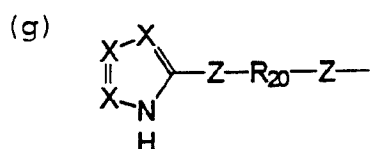
(e)



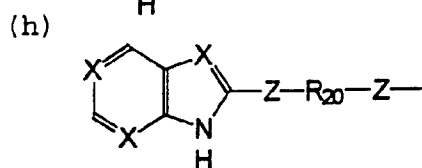
;



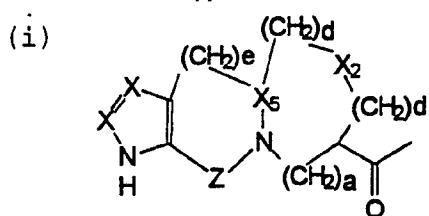
;



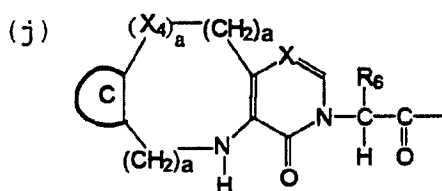
;



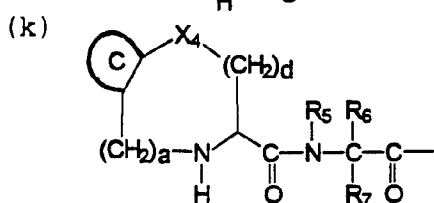
;



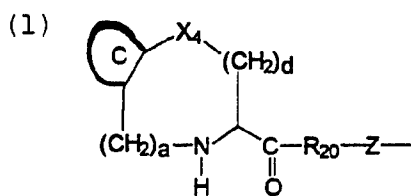
;



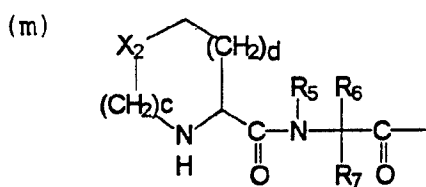
;



;

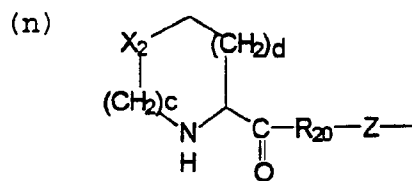


;

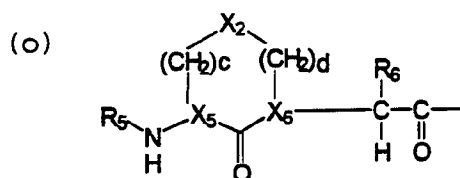


;

- 39 -

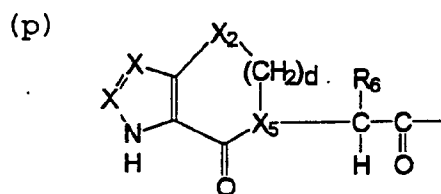


;

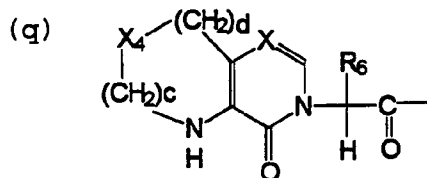


;

5

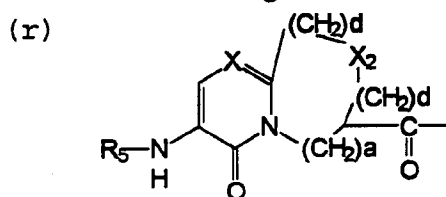


;

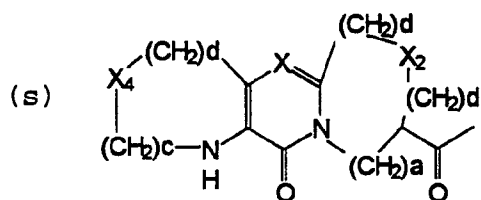


;

10

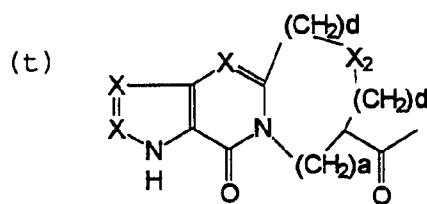


;



;

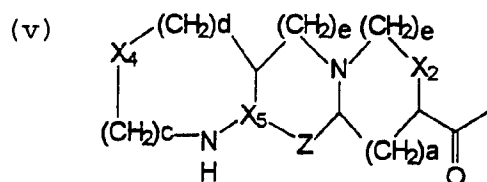
15



;

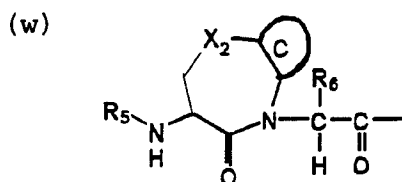
20

- 40 -

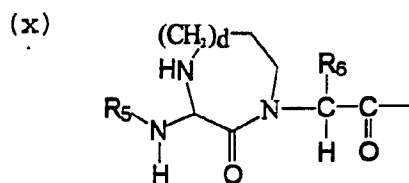


;

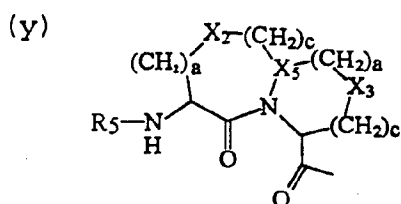
5



;



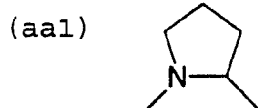
;



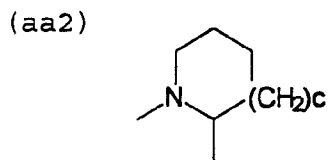
;

10

R_{20} is selected from the group consisting of:

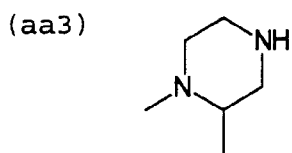


;



;

15

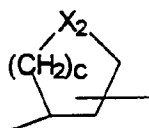


;

20

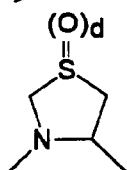
- 41 -

(aa4)



;

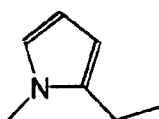
(aa5)



5

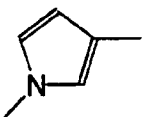
;

(bb)



;

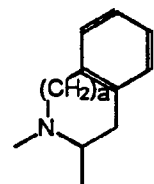
(cc)



;

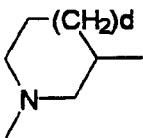
10

(dd)



;

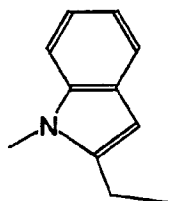
(ee)



15

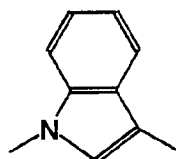
;

(ff)



;

(gg)

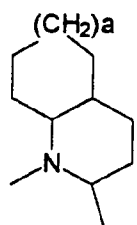


;

20

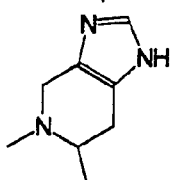
- 42 -

(gga)



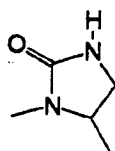
;

(ggb)



; and

(ggc)



;

wherein each ring C is independently chosen from
the group consisting of benzo, pyrido, thieno, pyrrolo,
furano, thiazolo, isothiazolo, oxazolo, isoxazolo,
pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R₃ is

-CN,

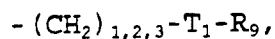
-CH=CH-R₉,-CH=N-O-R₉,-(CH₂)₁₋₃-T₁-R₉,-CJ₂-R₉,-CO-R₁₃, or
$$\begin{array}{c} \text{CO} \\ \text{CO} \end{array} \begin{array}{c} \text{N} \\ \text{N} \end{array} \begin{array}{c} \text{R}_5 \\ \text{R}_{10} \end{array}$$

each R₄ is independently selected from the group
consisting of:

-H,

-Ar₁,-R₉,-T₁-R₉, and

- 43 -

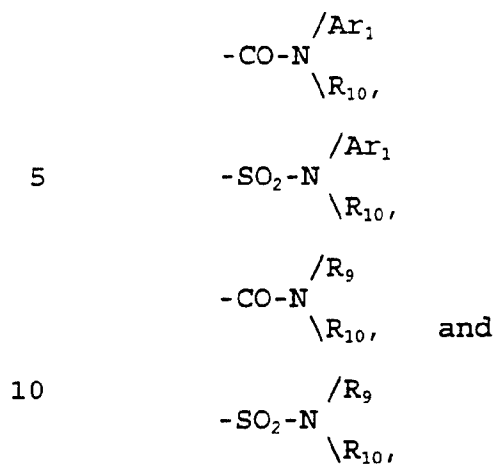


each T_1 is independently selected from the group consisting of:

- CH=CH-,
- 5 -O-,
- S-,
- SO-,
- SO₂-,
- NR₁₀-,
- 10 -NR₁₀-CO-,
- CO-,
- O-CO-,
- CO-O-,
- CO-NR₁₀-,
- 15 -O-CO-NR₁₀-,
- NR₁₀-CO-O-,
- NR₁₀-CO-NR₁₀-,
- SO₂-NR₁₀-,
- NR₁₀-SO₂-, and
- 20 -NR₁₀-SO₂-NR₁₀-,

each R_9 is independently selected from the group consisting of:

- H,
- Ar₁,
- 25 -CO-Ar₁,
- SO₂-Ar₁,
- CO-NH₂,
- SO₂-NH₂,
- R₉,
- 30 -CO-R₉,
- CO-O-R₉,
- SO₂-R₉,



R₆ and R₇ taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-; or

R₇ is -H and R₆ is:
 -H,
 -Ar₁,
 -R₉,
 20 - (CH₂)_{1,2,3}-T₁-R₉, or
 an α-amino acid side chain residue;

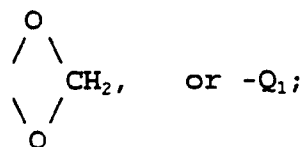
each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one or two Ar₁ groups;

each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

each R_{13} is independently selected from the group
30 consisting of $-Ar_2$, $-R_4$ and $-N-OH$
 $\begin{array}{c} \diagdown \\ R_5 \end{array} ;$

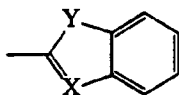
- 45 -

each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH, -perfluoro C₁₋₃ alkyl,

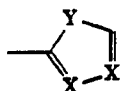


each Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ and -Q₂:

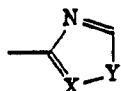
25 (hh)



(ii)



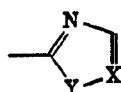
(jj)



30

, and

(kk)



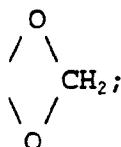
;

- 46 -

each Q_1 is independently selected from the group consisting of

- 5 $-Ar_1$
 $-O-Ar_1$
 $-R_9,$
 $-T_1-R_9,$ and
 $-(CH_2)_{1,2,3}-T_1-R_9;$

each Q_2 is independently selected from the group consisting of $-OH,$ $-NH_2,$ $-CO_2H,$ $-Cl,$ $-F,$ $-Br,$ $-I,$
 10 $-NO_2,$ $-CN,$ $-CF_3,$ and



15 provided that when $-Ar_1$ is substituted with a Q_1 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1 ;

20 each X is independently selected from the group consisting of $=N-$, and $=CH-$;

each X_2 is independently selected from the group consisting of $-O-$, $-CH_2-$, $-NH-$, $-S-$, $-SO-$, and $-SO_2-$;

each X_3 is independently selected from the group consisting of $-CH_2-$, $-S-$, $-SO-$, and $-SO_2-$;

25 each X_4 is independently selected from the group consisting of $-CH_2-$ and $-NH-$;

each X_5 is independently selected from the group consisting of $-CH-$ and $-N-$;



- 47 -

X_6 is CH or N, provided that when X_6 is N in the R_1 group labeled (o) and X_5 is CH and X_2 is CH_2 the ring of the R_1 group labeled (o) must be substituted by Q_1 or benzofused;

5 each Y is independently selected from the group consisting of -O- and -S-, and -NH;

each Z is independently CO or SO_2 ,

each a is independently 0 or 1,

each c is independently 1 or 2,

10 each d is independently 0, 1, or 2, and

each e is independently 0, 1, 2, or 3,

provided that when

R_1 is (f),

R_6 is an α -amino acid side chain residue, and

15 R_7 is -H,

then (aa1) and (aa2) must be substituted with Q_1 ;

also provided that when

R_1 is (o),

g is 0,

20 J is -H,

m is 1,

R_6 is an α -amino acid side chain residue,

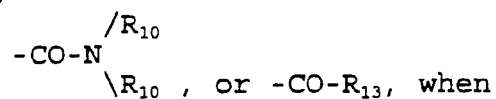
R_7 is -H,

X_2 is $-CH_2-$,

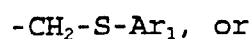
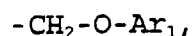
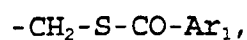
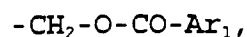
25 X_5 is $-CH-$,

X_6 is $-N-$, and

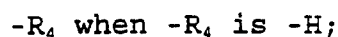
- 48 -

R₃ is

5

R₁₃ is:

10



then the ring of the R₁(o) group must be substituted with Q₁ or benzofused; and

provided that when

15

R₁ is (w),

g is 0,

J is -H,

m is 1,

T is -CO₂H or -CO-NH-OH,X₂ is O,

20

R₅ is benzyloxycarbonyl, and

ring C is benzo,

then R₃ cannot be -CO-R₁₃ when:R₁₃ is -CH₂-O-Ar₁ and

25

Ar₁ is 1-phenyl-3-chloro- or
3-trifluoromethyl-pyrazole-5-yl;

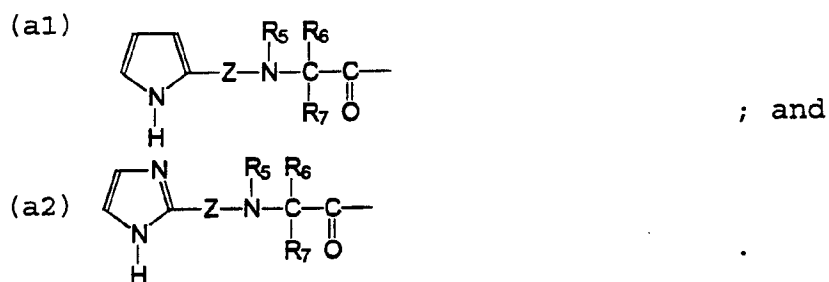
or when

R₁₃ is -CH₂-O-CO-Ar₁ andAr₁ is 2,6-dichlorophenyl.

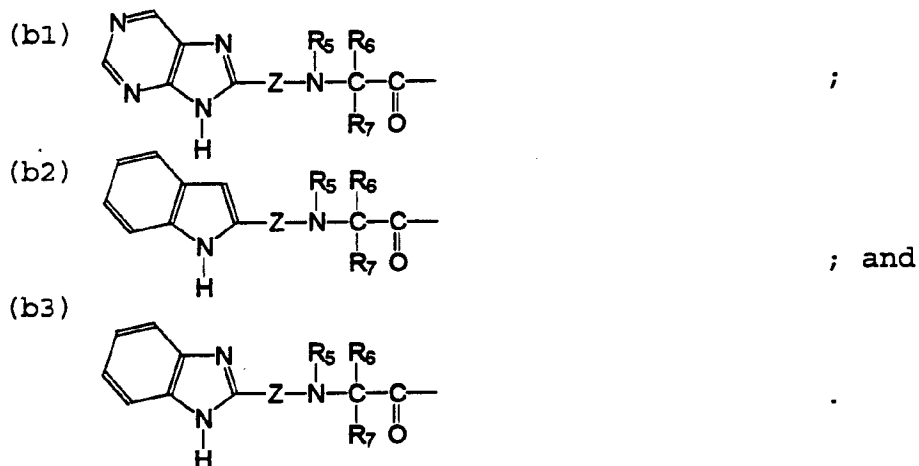
30

Preferred forms of the R₁ group (a) for
embodiments A and B are:

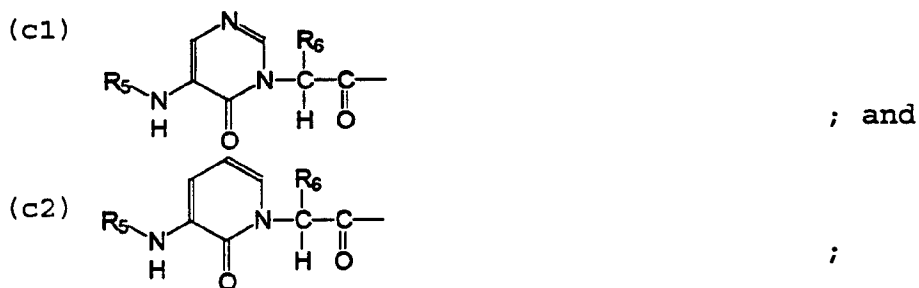
- 49 -



5

Preferred forms of the R₁ group (b) are:

10

Preferred forms of the R₁ group (c) are:

15

provided that when R₁ is (c1),

20

g is 0,

J is -H,

m is 1,

T is -CO₂H,

X is N,

25

R₅ is benzyloxycarbonyl, andR₆ is -H,

- 50 -

then R_3 cannot be $-\text{CO}-R_{13}$ when

R_{13} is $-\text{CH}_2-\text{O}-\text{Ar}_1$ and

Ar_1 is a chloro-substituted 1-phenyl-3-trifluoromethyl-pyrazole-5-yl, or when

5

R_{13} is $-\text{CH}_2-\text{O}-\text{CO}-\text{Ar}_1$ and

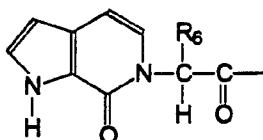
Ar_1 is 2,6-dichlorophenyl,

and when the 2-position of the scaffold ring is substituted with para-fluoro-phenyl;

10

Preferred forms of the R_1 group (d) are:

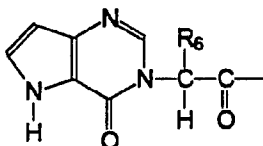
(d1)



;

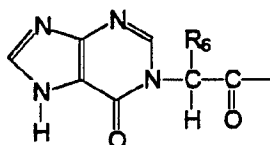
15

(d2)



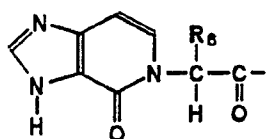
;

(d3)



; and

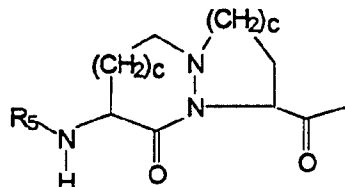
(d4)



20

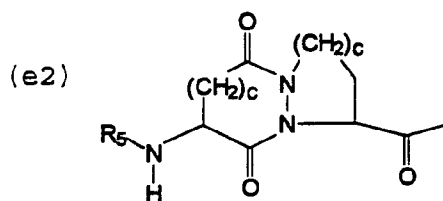
Preferred forms of the R_1 group (e) are:

(e1)

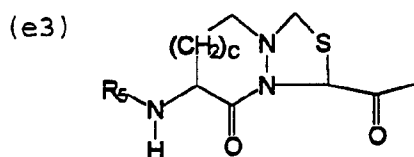


;

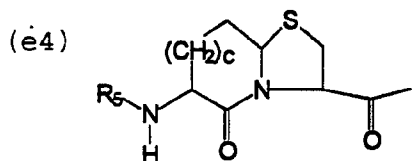
25



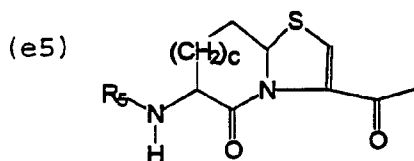
;



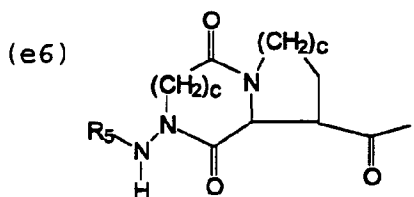
;



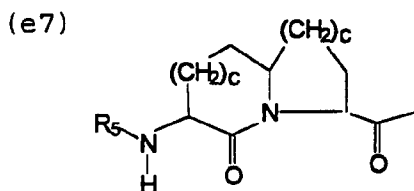
;



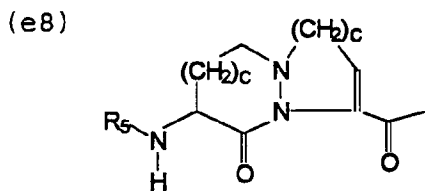
;



;



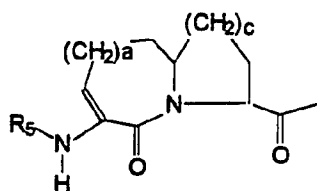
which is optionally benzofused;



; and

- 52 -

(e9)



provided that when R_1 is (e4),

5

g is 0,

J is -H,

m is 1,

T is $-\text{CO}_2\text{H}$,

R_5 is benzyloxycarbonyl, and

10

c is 1,

then R_3 cannot be $-\text{CO}-R_{13}$ when

R_{13} is $-\text{CH}_2-\text{O}-\text{Ar}_1$ and

Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl, wherein the phenyl is optionally substituted with a chlorine atom; or when

15

R_{13} is $-\text{CH}_2-\text{O}-\text{CO}-\text{Ar}_1$ and

Ar_1 is 2,6-dichlorophenyl,

and when the 2-position of the scaffold ring is substituted with para-fluoro-phenyl; and

20

also provided that when

R_1 is (e7),

g is 0,

J is -H,

m is 1,

25

T is $-\text{CO}_2\text{H}$ or $-\text{CO}-\text{NH}-\text{OH}$,

R_5 is a protective group for the N atom of an amino acid side chain residue, and each c is 1,

then R_3 cannot be $-\text{CO}-R_{13}$ when

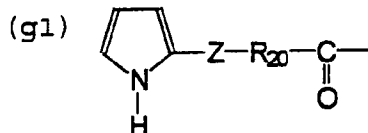
30

R_{13} is:

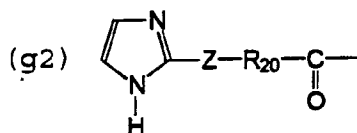
- 53 -

-CH₂-O-CO-Ar₁,
 -CH₂-S-CO-Ar₁,
 -CH₂-O-Ar₁, or
 -CH₂-S-Ar₁.

5 Preferred forms of the R₁ group (g) are:

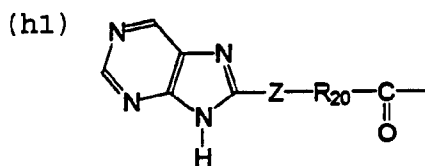


; and



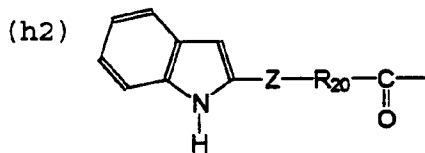
10

Preferred forms of the R₁ group (h) are:

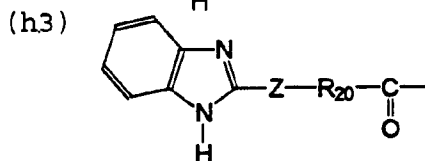


15

;

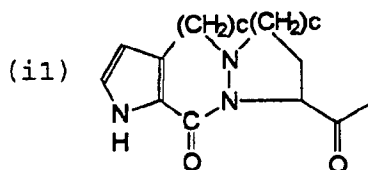


; and

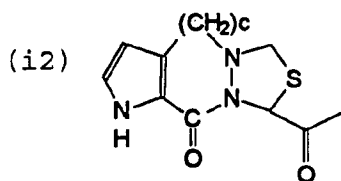


20

Preferred forms of the R₁ group (i) are:



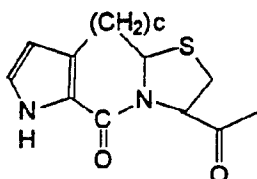
;



;

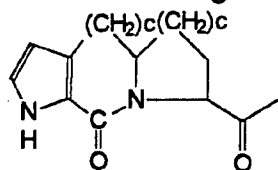
- 54 -

(i3)



; and

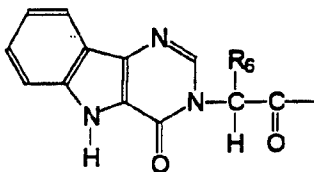
(i4)



5

Preferred forms of the R₁ group (j) are:

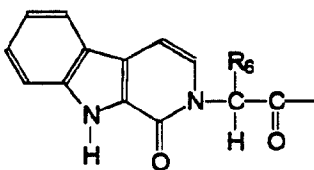
(j1)



;

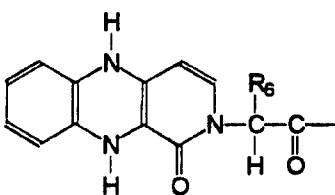
10

(j2)



;

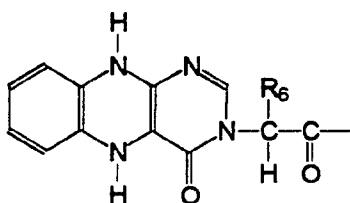
(j3)



; and

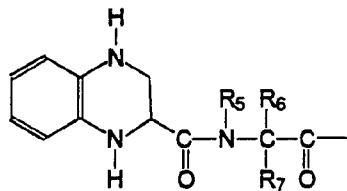
15

(j4)

Preferred forms of the R₁ group (k) are:

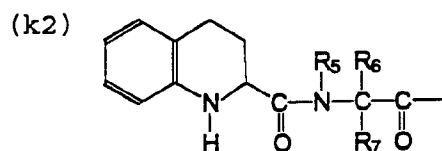
20

(k1)

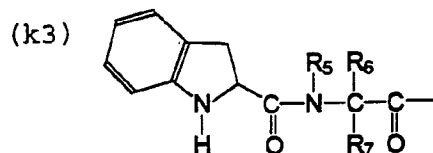


;

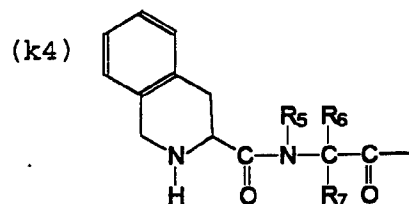
- 55 -



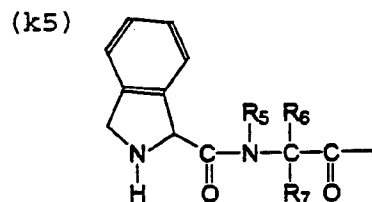
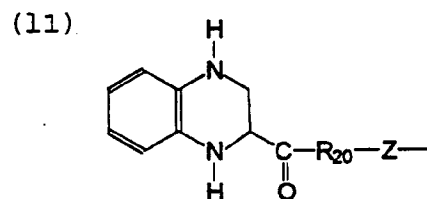
;



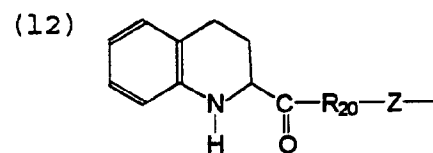
;



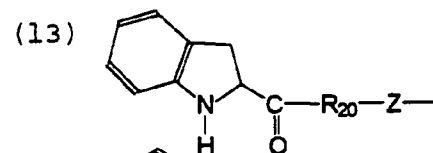
; and

Preferred forms of the R₁ group (1) are:

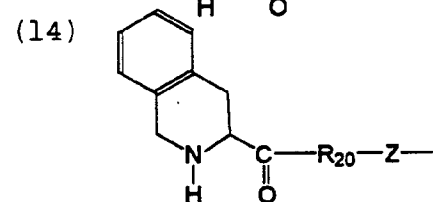
;



;

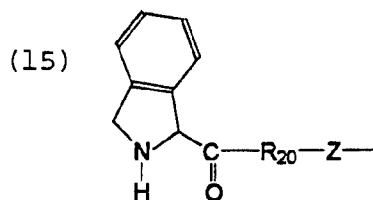


;

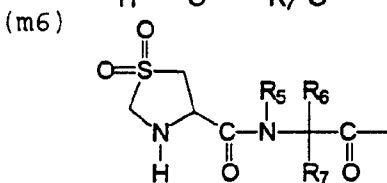
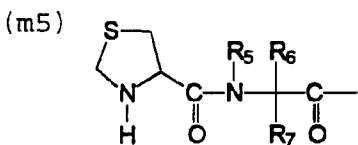
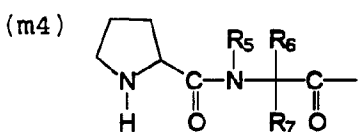
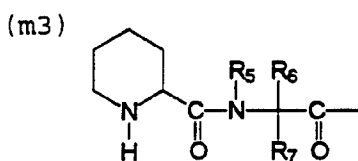
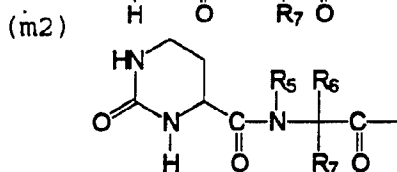
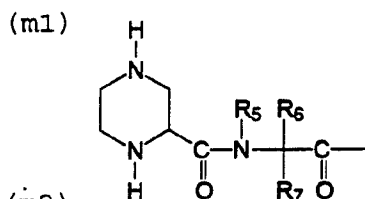


; and

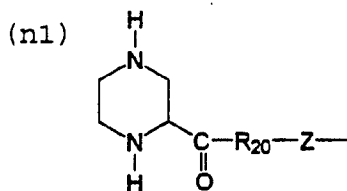
- 56 -



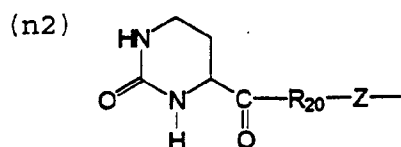
Preferred forms of the R_1 group (m) are:



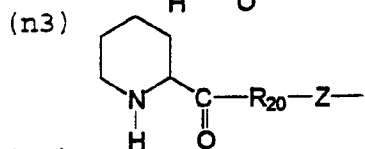
Preferred forms of the R_1 group (n) are:



- 57 -

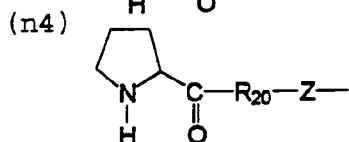


;

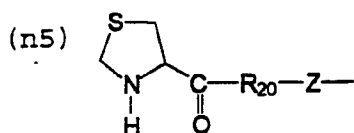


;

5

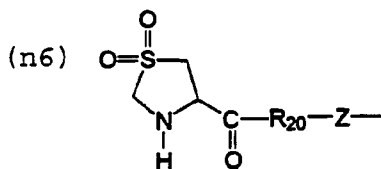
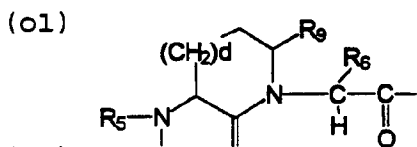


;



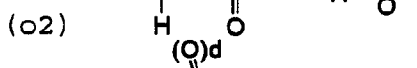
; and

10

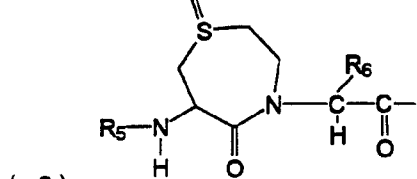
Preferred forms of the R₁ group (o) are:

;

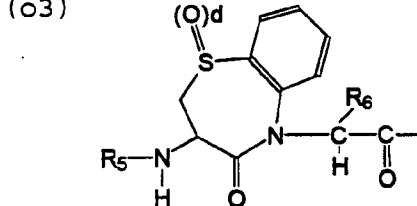
15



;



;

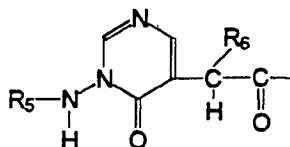


; and

20

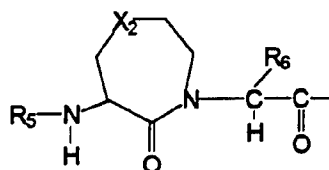
- 58 -

(o5)



5 A preferred form of the R₁ group (o) of
embodiment B is:

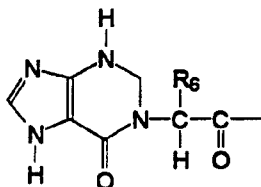
(o6)



wherein X₂ is -O-, -S-, -SO₂-, or -NH-.

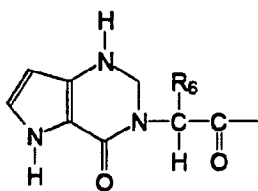
10 For embodiments A and B, preferred forms of
the R₁ group (p) are:

(p1)



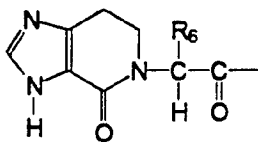
;

(p2)



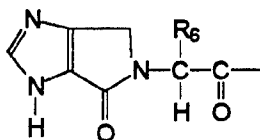
;

(p3)



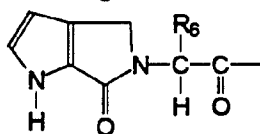
;

(p4)



; and

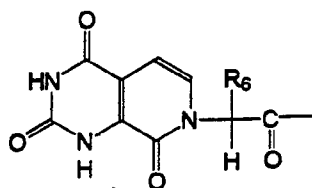
(p5)



- 59 -

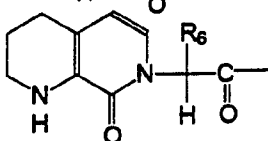
Preferred forms of the R₁ group (q) are:

(q1)



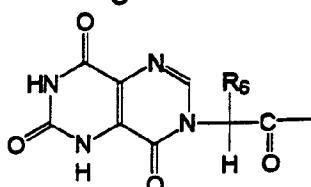
;

(q2)



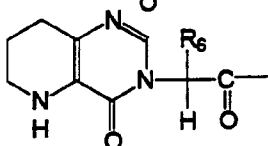
;

(q3)



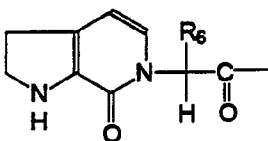
;

(q4)



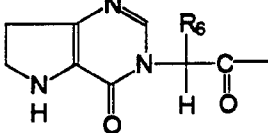
;

(q5)

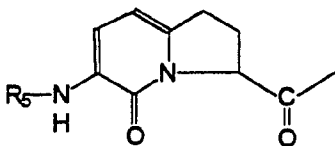


; and

(q6)

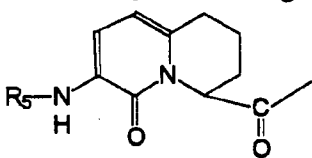
Preferred forms of the R₁ group (r) are:

(r1)



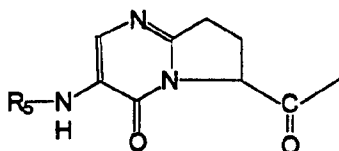
;

(r2)



;

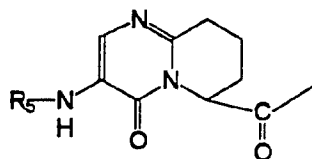
(r3)



;

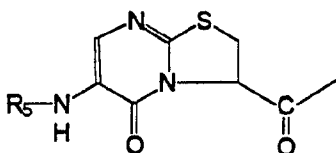
- 60 -

(r4)



;

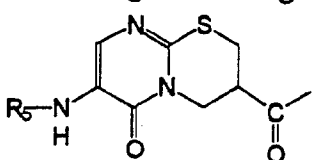
(r5)



;

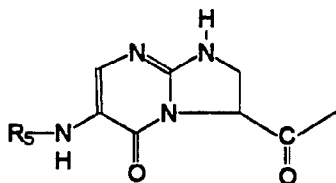
5

(r6)



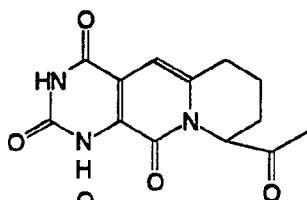
; and

(r7)

Preferred forms of the R₁ group (s) are:

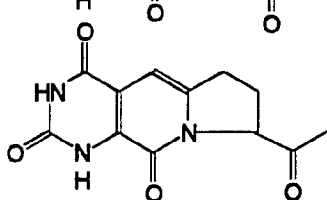
10

(s1)



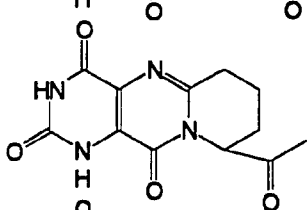
;

(s2)



;

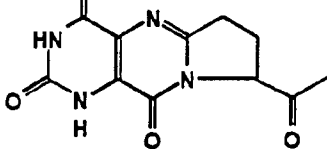
(s3)



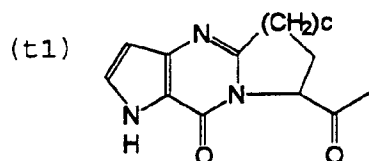
; and

15

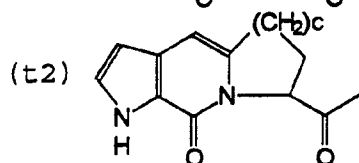
(s4)



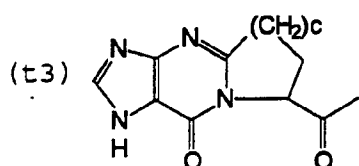
- 61 -

Preferred forms of the R₁ group (t) are:

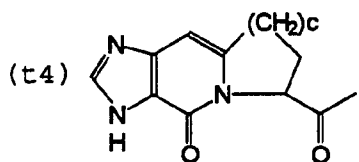
;



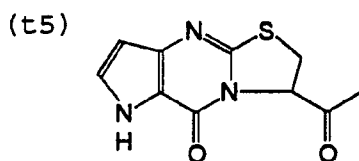
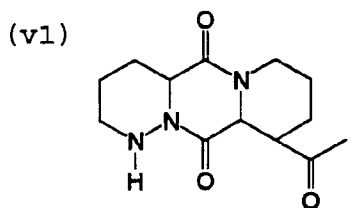
;



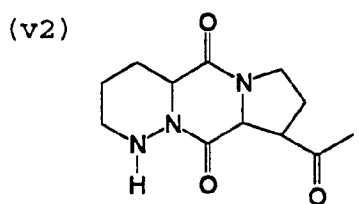
;



; and

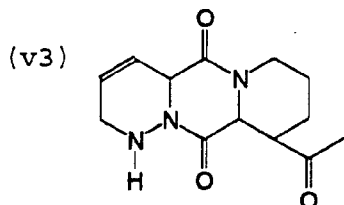
Preferred forms of the R₁ group (v) are:

;

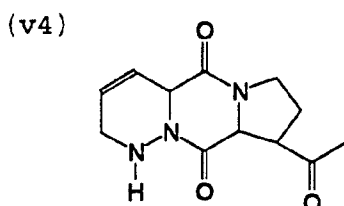


;

- 62 -



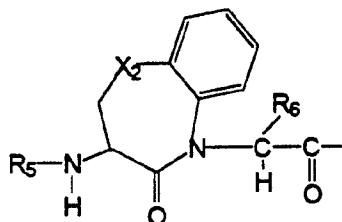
; and



5

A preferred form of the R1 group (w) of embodiment B is:

(w1)



10

wherein X_2 is -O-, -S-, -SO₂- or -NH-.

The preferred compounds of embodiments A and B of this invention are those which employ formula α , wherein:

15 X_1 is CH;

g is O;

J is -H;

m is 0 or 1 and T is -Ar₃, -CO-CO₂H, -CO₂H or any bioisosteric replacement for -CO₂H, or

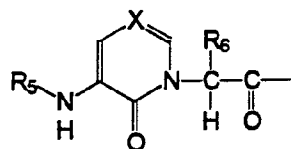
20 m is 1 or 2 and T is -OH, -CF₃, or -CO₂H;

more preferably m is 1 and T is -CO₂H;

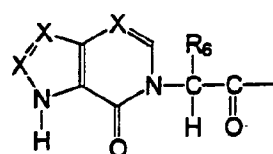
- 63 -

 R_1 is

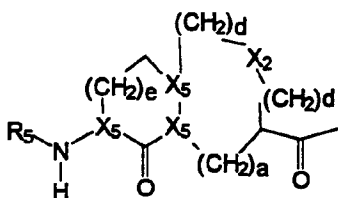
(c)



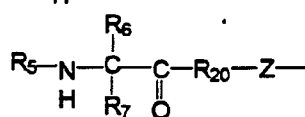
(d)



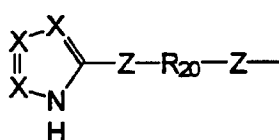
(e)



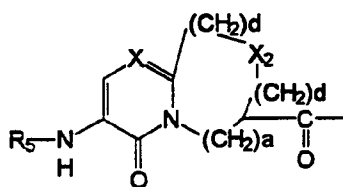
(f)



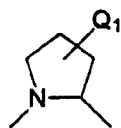
(g)



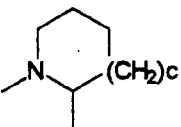
(r)

 R_{20} is

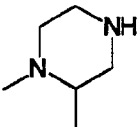
(aa1)



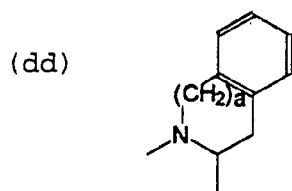
(aa2)



(aa3)



- 64 -



wherein ring C is benzo;

R_3 is

5 $-\text{CO}-R_{13}$, or
 $-\text{CO}-\text{CO}-\text{N} \begin{matrix} /R_5 \\ \backslash R_{10} \end{matrix}$;

most preferably R_3 is any one of 1), 2) or 3) as
 10 follows: 1) $-\text{CO}-\text{Ar}_2$, 2) $-\text{CO}-R_9$ where R_9 is C_{3-6} alkyl
 substituted with two Ar_1 groups or one Ar_1 group itself
 substituted with an Ar_1 group, $-\text{C}_{1-2}-\text{Ar}_1$, $-\text{Cl}$, $-\text{CH}_3$, or
 $-\text{CF}_3$, or 3) $-(\text{CH}_2)_{1,2}-\text{T}_1-R_9$ where T_1 is $-\text{O}-$ or $-\text{S}-$ and R_9
 15 is C_{1-2} alkyl substituted with two Ar_1 groups or one Ar_1
 group itself substituted with an Ar_1 group, $\text{C}_{1-2}-\text{Ar}_1$,
 $-\text{Cl}$, $-\text{CH}_3$, or $-\text{CF}_3$;

R_4 is $-\text{H}$ or $-\text{R}_9$;

T_1 is

20 $-\text{O}-$,
 $-\text{S}-$,
 $-\text{CO}-$,
 $-\text{O}-\text{CO}-$, or
 $-\text{SO}_2-$;

when R_1 is (a), (b), (k), or (m), R_5 is preferably
 25 $-\text{Ar}_1$ or $\text{C}_{1-4}-\text{Ar}_1$;

- 65 -

when R_1 is (c), (e), (f), (o), or (r), R_5 is preferably $-\text{SO}_2-\text{Ar}_1$, $-\text{SO}_2-\text{R}_9$, or $-\text{CO}-\text{C}_{1-4}-\text{Ar}_1$;

R_7 is $-\text{H}$ and R_6 is $\text{C}_{1-4}-\text{Ar}_1$;

5 R_{10} is $-\text{H}$ or a C_{1-3} straight or branched alkyl group;

R_{13} is $-\text{Ar}_2$;

Ar_1 is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl;

10 Ar_2 is preferably substituted with $-\text{Ar}_1$, or $-\text{C}_{1-4}-\text{Ar}_1$;

Ar_3 is phenyl, thiophene, thiazole, pyridine, or oxazole; and

15 Q_1 is $-\text{R}_9$ or $-(\text{CH}_2)_{1,2}-\text{T}_1-(\text{CH}_2)_{1-3}-\text{Ar}_1$ where T_1 is $-\text{O}-$ or $-\text{S}-$.

In connection with this continuation-in-part, we now prefer the compounds of embodiment B of this invention which employ formula α , wherein:

X_1 is $-\text{CH}$;

20 g is O ;

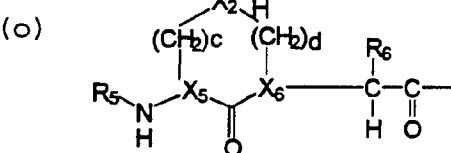
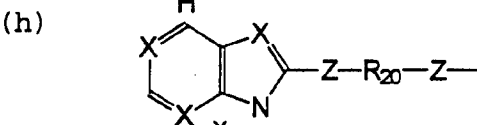
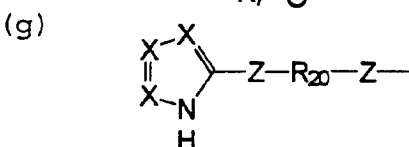
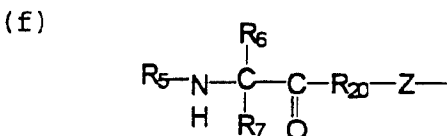
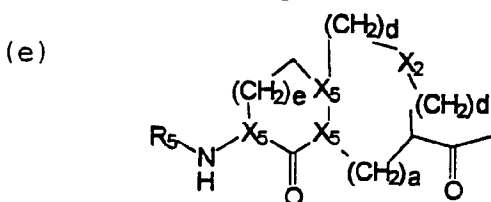
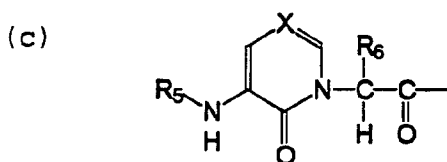
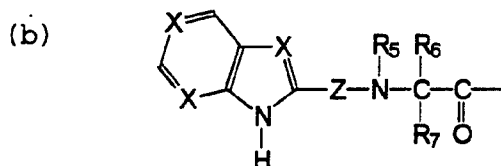
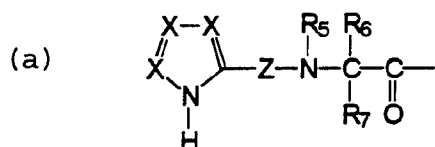
J is $-\text{H}$;

m is 0 or 1 and T is $-\text{CO}-\text{CO}_2\text{H}$, or any bioisosteric replacement for $-\text{CO}_2\text{H}$; or

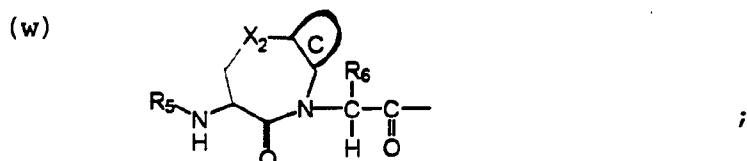
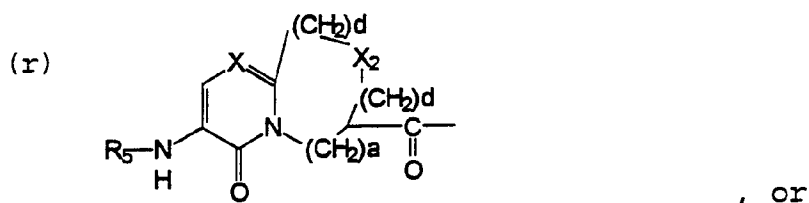
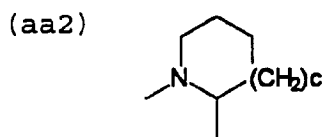
- 66 -

m is 1 and T is $-\text{CO}_2\text{H}$;

R_1 is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q_1 , at
 5 any nitrogen by R_5 , or at any atom by $=\text{O}$, $-\text{OH}$, $-\text{CO}_2\text{H}$, or halogen, and wherein (e) is optionally benzofused:

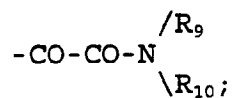


- 67 -

R₂₀ is

and c is 1;

ring C is benzo optionally substituted with
-C₁₋₃ alkyl, -O-C₁₋₃ alkyl, -Cl, -F or -CF₃;

R₃ is:-CO-R₁₃, or

more preferably R₃ is any one of 1), 2) or 3) as follows: 1) -CO-Ar₂; 2) -CO-R₉ where R₉ is C₁₋₅ alkyl substituted with an Ar₁; or 3) -CH₂-T₁-R₉ where T₁ is -O- or -S- and R₉ is C₁₋₂ alkyl substituted with one Ar₁ group;

R₄ is -H or -R₉;

- 68 -

T₁ is:

5 -O-,
 -S-,
 -CO-,
 -O-CO-, or
 -SO₂-;

when R₁ is (a) or (b), R₅ is preferably -H, and
when R₁ is (c), (e), (f), (o), (r), (w), (x) or
(y), R₅ is preferably:

10 -CO-Ar₁
 -SO₂-Ar₁,
 -CO-NH₂,
 -CO-NH-Ar₁
 -CO-R₉,
15 -CO-O-R₉,
 -SO₂-R₉, or
 -CO-NH-R₉,

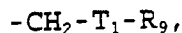
20 R₇ is -H and R₆ is
 -H,
 -R₉ or
 -Ar₁;

25 R₉ is C₁₋₆ straight or branched alkyl group
 optionally substituted with =O and optionally
 substituted with -Ar₁;

 R₁₀ is -H or a C₁₋₃ straight or branched alkyl
 group;

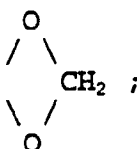
30 R₁₃ is:
 -H,
 -R₉,
 -Ar₂, or

- 69 -



more preferably where $-\text{Ar}_2$ is
 (hh) and where (hh) is optionally substituted singly or
 multiply with $-\text{C}_{1-6}$ alkyl, $-\text{O}-\text{C}_{1-6}$ alkyl,
 5 $-\text{NH}-\text{C}_{1-6}$ alkyl, $-\text{N}-(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{S}-\text{C}_{1-6}$ alkyl, $-\text{Cl}$,
 $-\text{F}$, $-\text{CF}_3$, or

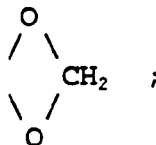
10



15

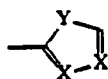
Ar_1 is phenyl, naphthyl, pyridyl, benzothiazolyl,
 thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or
 indolyl substituted with $-\text{O}-\text{C}_{1-3}$ alkyl, $-\text{NH}-\text{C}_{1-3}$ alkyl, -
 N- $(\text{C}_{1-3} \text{ alkyl})_2$, $-\text{Cl}$, $-\text{F}$, $-\text{CF}_3$,
 $-\text{C}_{1-3}$ alkyl, or

20

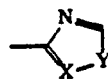


preferably where Ar_2 is:

(ii)



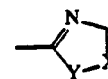
(jj)



25

, or

(kk)



30

each X is independently selected from the group
 consisting of $=\text{N}-$, and $=\text{CH}-$;

- 70 -

each X_2 is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

each X_5 is independently selected from the group consisting of -CH- and -N-;

5

X_6 is -CH- or -N-; and

Z is C=O;

10 provided that when

R_1 is (f),

R_6 is an α -amino acid side chain residue, and

R_7 is -H,

then (aa1) and (aa2) must be substituted with Q_1 ;

15

also provided that when

R_1 is (o),

g is 0,

J is -H,

20

m is 1,

R_6 is an α -amino acid side chain residue,

R_7 is -H,

X_2 is -CH₂-,

25

X_5 is -CH- ,

X_6 is -N- , and

30

R_3 is

$\begin{array}{c} /R_{10} \\ -CO-N \\ \backslash R_{10} \end{array}$, or
-CO- R_{13} , when

35

- 71 -

R₁₃ is:

- 5 -CH₂-O-CO-Ar₁,
 -CH₂-S-CO-Ar₁,
 -CH₂-O-Ar₁,
 -CH₂-S-Ar₁, or
 -R₄ when -R₄ is -H;

then the ring of the R₁(o) group must be substituted with Q₁ or benzofused; and

provided that when

- 10 R₁ is (w),
 g is 0,
 J is -H,
 m is 1,
 T is -CO₂H,
15 X₂ is O,
 R₅ is benzyloxycarbonyl, and
 ring C is benzo,
then R₃ cannot be -CO-R₁₃ when:
 R₁₃ is -CH₂-O-Ar₁ and
20 Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl,
wherein the phenyl is optionally substituted with a chlorine atom;
 or when R₁₃ is -CH₂-O-CO-Ar₁, wherein
Ar₁ is 2,6-dichlorophenyl.

- 25 A preferred form of R₁₃ is -CH₂-O-R₉, wherein
R₉ is a C₁₋₆ straight or branched alkyl group optionally substituted with =O and optionally substituted with Ar₁;

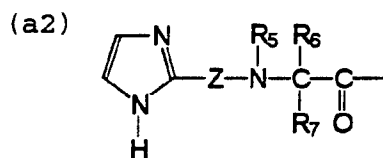
- another preferred form of R₁₃ is CH₂-S-R₉, wherein
R₉ is a C₁₋₆ straight or branched alkyl group optionally
30 substituted with Ar₁;

- 72 -

another preferred form of R_{13} is $\text{CH}_2\text{-O-}R_9$ wherein R_9 is a C_{1-6} straight or branched alkyl group optionally substituted with Ar_1 ;

another preferred form of R_{13} is H.

5 A more preferred form of the R_1 group (a) is:

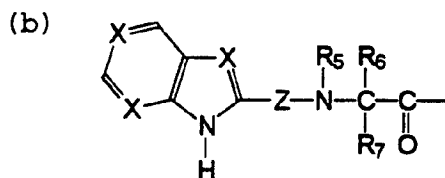


optionally substituted with Q_1 , wherein R_5 is -H;

R_7 is -H; and

10 Z is C=O;

a more preferred form of the R_1 group (b) is:

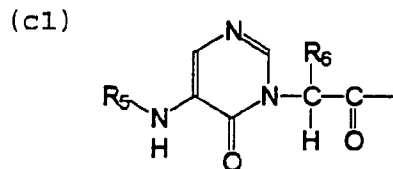


optionally substituted with Q_1 , wherein R_5 is -H;

15 R_7 is -H; and

Z is C=O;

more preferred forms of the R_1 group (c) are:

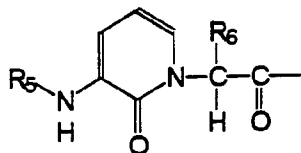


20

, and

- 73 -

(c2)

provided that when R_1 is (c1),

g is 0,

J is -H,

m is 1,

T is $-\text{CO}_2\text{H}$,

X is N,

 R_5 is benzyloxycarbonyl, and R_6 is -H,then R_3 cannot be $-\text{CO}-R_{13}$ when R_{13} is $-\text{CH}_2-\text{O}-\text{Ar}_1$ and

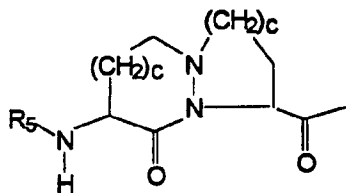
Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with a chlorine atom; or when

 R_{13} is $-\text{CH}_2-\text{O}-\text{CO}-\text{Ar}_1$, wherein Ar_1 is 2,6-dichlorophenyl,

and wherein the 2-position of the scaffold ring is substituted with para-fluoro-phenyl;

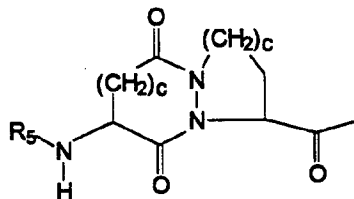
more preferred forms of the R_1 group (e) are:

(e1)



, and

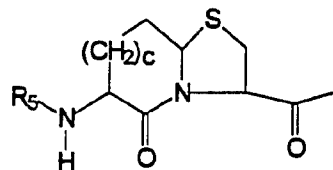
(e2)



wherein c is 2; and

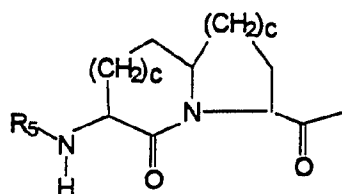
- 74 -

(e4)



, and

(e7)



which is optionally
benzofused,

wherein c is 1 or 2;

provided that when R₁ is (e4),

10

g is 0,

J is -H,

m is 1,

T is -CO₂H,

R₅ is benzyloxycarbonyl, and

15

c is 1,

then R₃ cannot be -CO-R₁₃ when

R₁₃ is -CH₂-O-Ar₁ and

Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with a chlorine atom; or when

20

R₁₃ is -CH₂-O-CO-Ar₁, wherein

Ar₁ is 2,6-dichlorophenyl,

and wherein the 2-position of the scaffold ring is substituted with para-fluoro-phenyl; and

25

also provided that when

R₁ is (e7),

g is 0,

J is -H,

m is 1,

- 75 -

T is $-\text{CO}_2\text{H}$, $-\text{CO}-\text{NH}-\text{OH}$, or a bioisosteric replacement for $-\text{CO}_2\text{H}$,

R_5 is a protective group for the N atom of an α -amino acid side chain residue, and

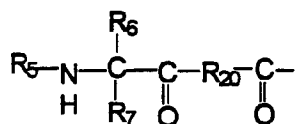
5 each c is 1,

then R_3 cannot be $-\text{CO}-\text{R}_{13}$ when

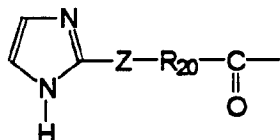
R_{13} is:

10 $-\text{CH}_2-\text{O}-\text{CO}-\text{Ar}_1$,
 $-\text{CH}_2-\text{S}-\text{CO}-\text{Ar}_1$,
 $-\text{CH}_2-\text{O}-\text{Ar}_1$, or
 $-\text{CH}_2-\text{S}-\text{Ar}_1$.

a more preferred form of the R_1 group (f) is
 (f1)



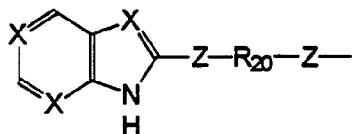
15 a more preferred form of the R_1 group (g) is:
 (g2)



R_{20} is (a1) optionally substituted singly or multiply with Q_1 ; and

20 Z is $\text{C}=\text{O}$;

a more preferred form of the R_1 group (h) is:
 (h)



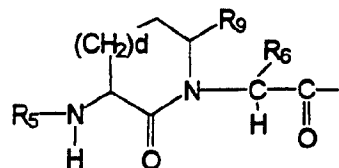
- 76 -

R_{20} is (aa1) optionally substituted singly or multiply with Q_1 ; and

Z is C=O;

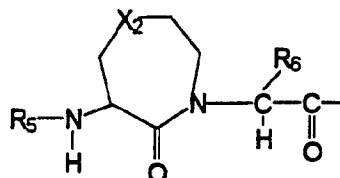
more preferred forms of the R_1 group (o) are:

5 (o1)



wherein d is 1 or 2; and

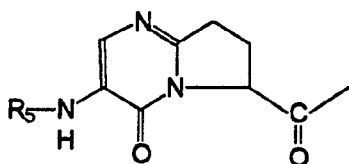
(o6)



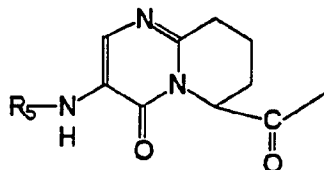
10

more preferred forms of the R_1 group (r) are:

(r3)

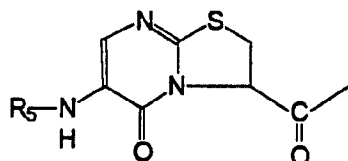


(r4)



15

(r5)

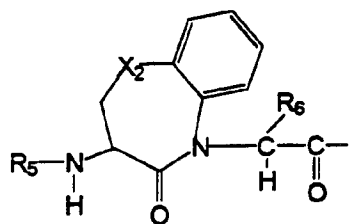


optionally substituted with Q_1 ;

- 77 -

a more preferred form of the R_1 group (w) is:

(w1)



; wherein

X_2 is:

5

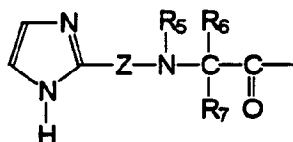
-NH-,
 -S- ,
 -O- , or
 -SO₂-;

optionally substituted with R_5 or Q_1 at X_2
 10 when X_2 is -N-; and

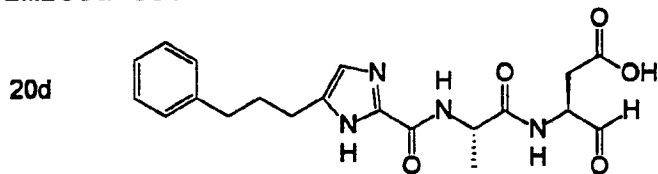
ring C is benzo substituted with -C₁₋₃ alkyl,
 -O-C₁₋₃ alkyl, -Cl, -F or -CF₃.

When R_1 is:

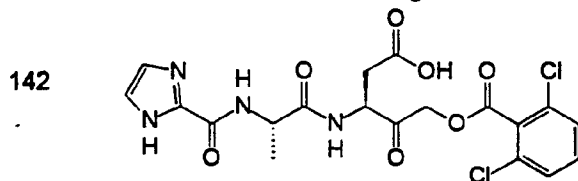
(a2)



15 preferred compounds of this invention include but are
 not limited to:



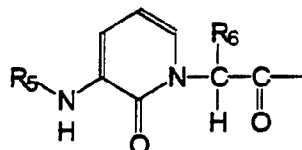
; and



- 78 -

A preferred compound of embodiment B of this invention employs formula α , wherein the R_1 is:

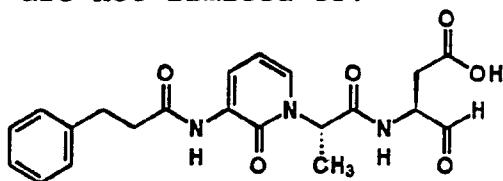
(c2)



5

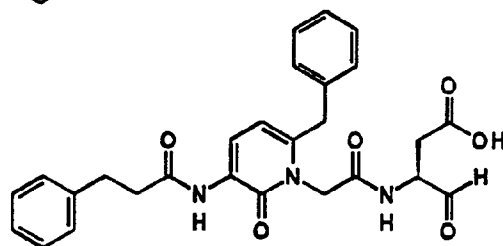
Preferred compounds of this embodiment include but are not limited to:

54a



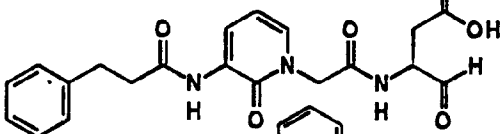
;

54b



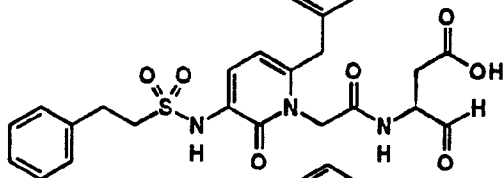
;

54g



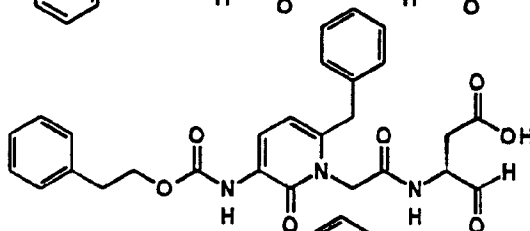
;

54j



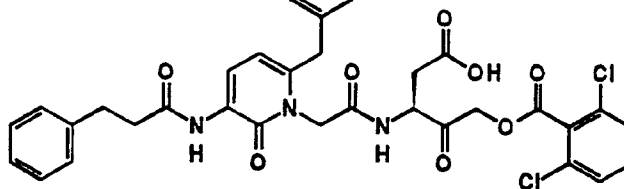
;

54k



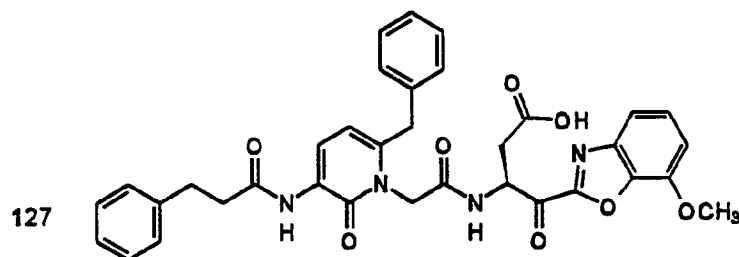
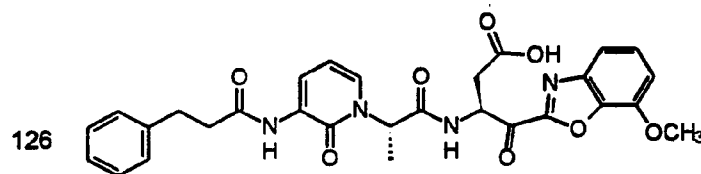
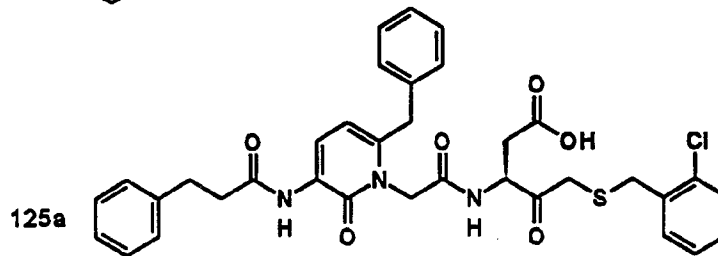
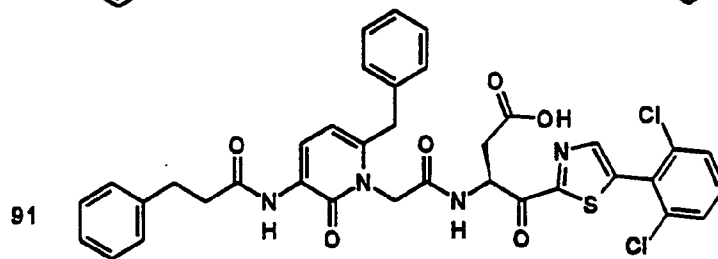
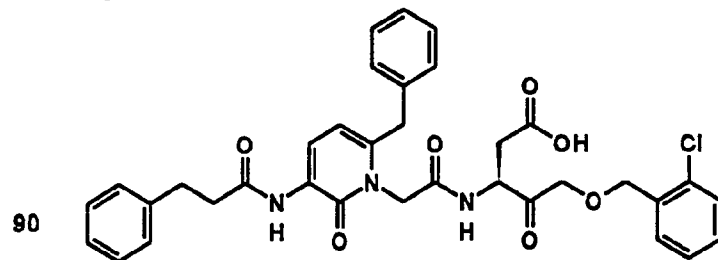
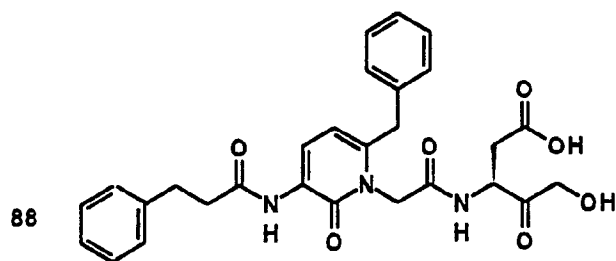
;

57b

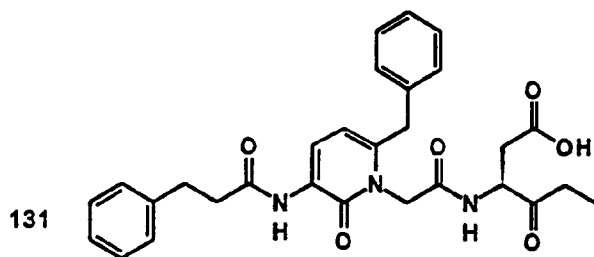
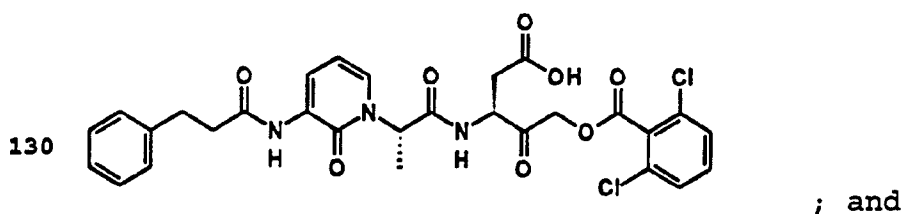
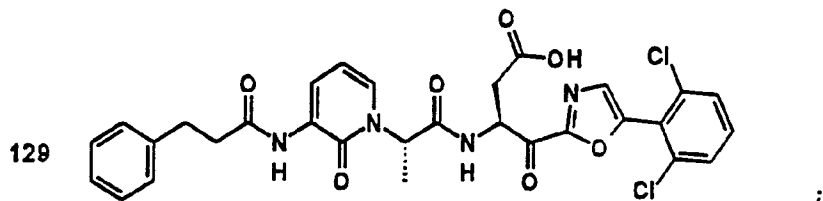
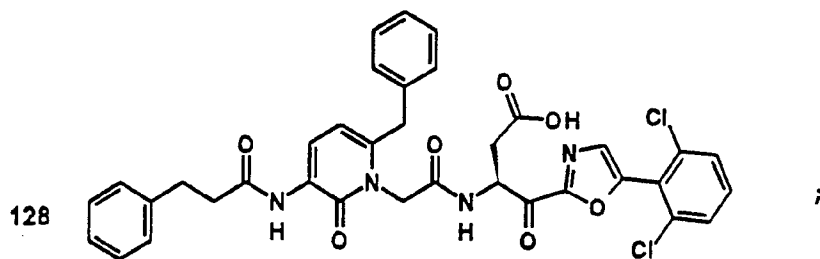


;

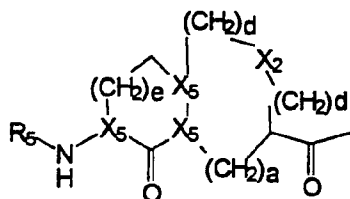
20



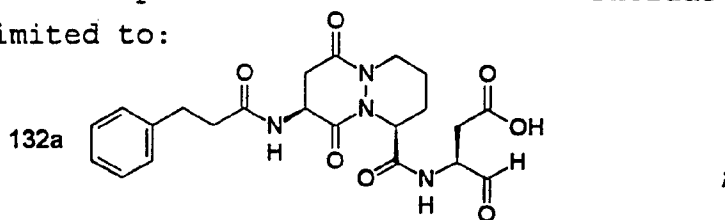
- 80 -

When R_1 is:

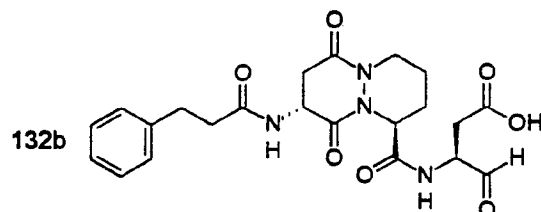
(e)



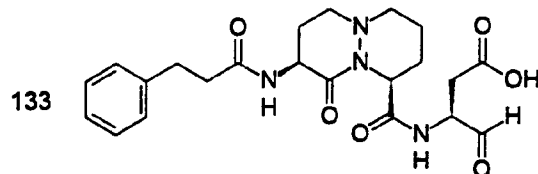
20 preferred compounds of this invention include but are not limited to:



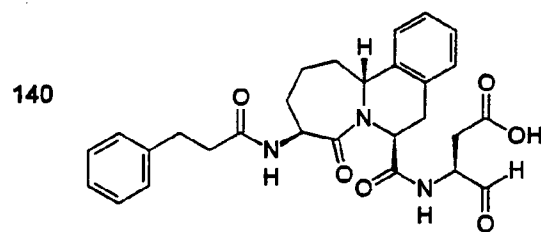
- 81 -



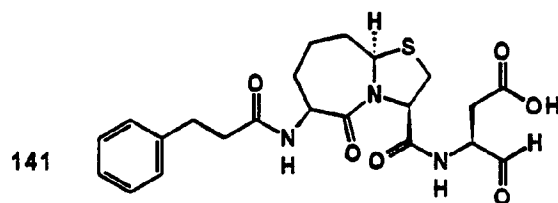
;



;



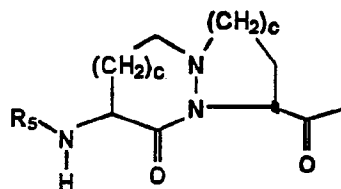
; and



A preferred compound of embodiment B of this invention employs formula α , wherein:

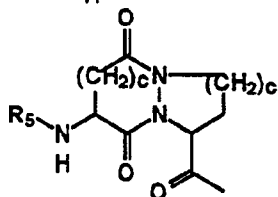
R_1 is:

(a1)



, or

(a2)



and c is 2;

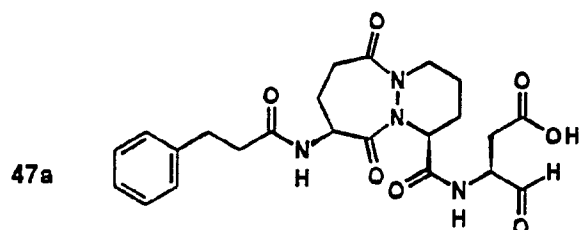
m is 1;

- 82 -

T is $-\text{CO}_2\text{H}$; and R_3 is $-\text{CO}-\text{R}_{13}$.

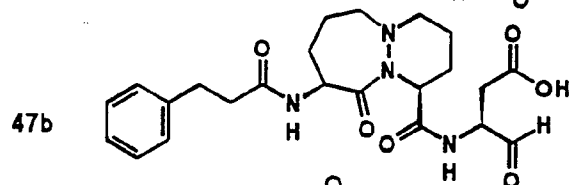
Preferred compounds of this embodiment
include but are not limited to:

5



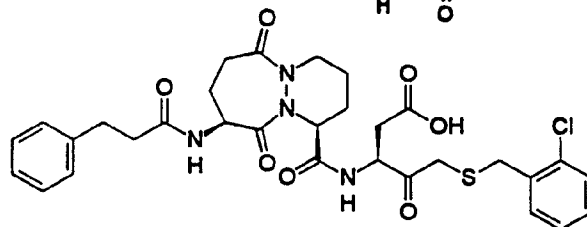
;

10



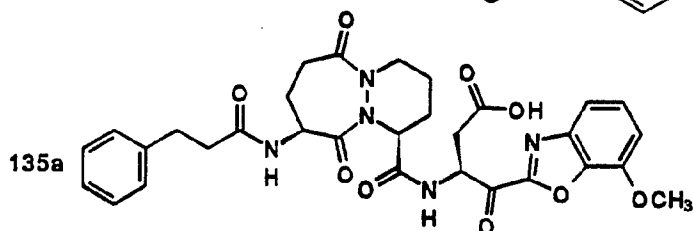
;

125b

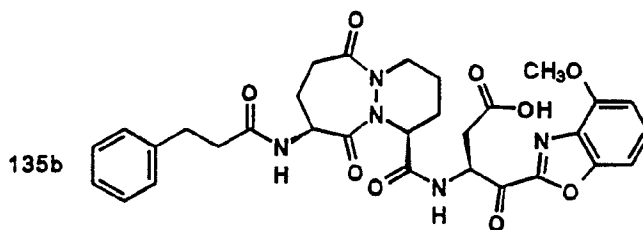


;

15

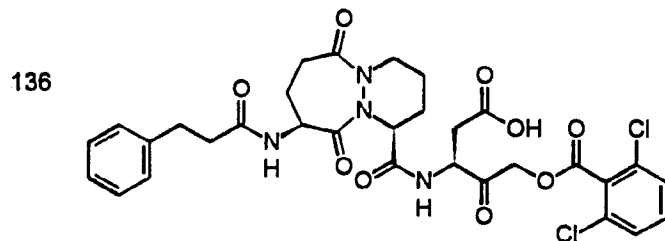


;



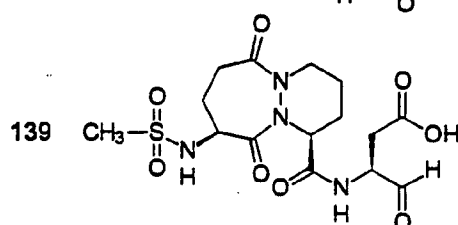
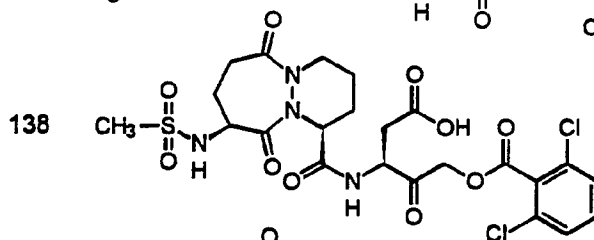
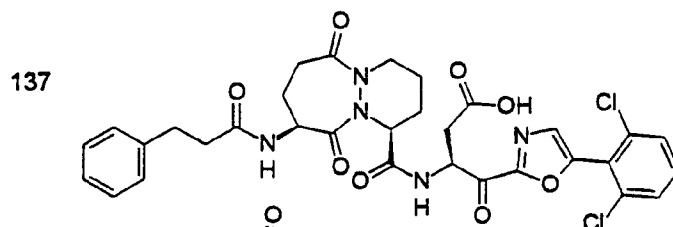
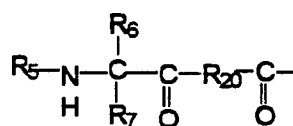
;

20

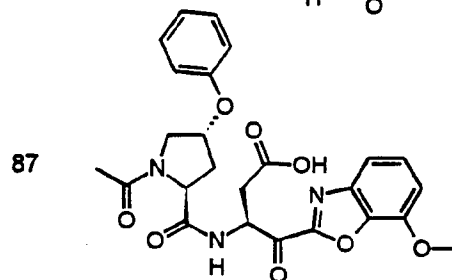
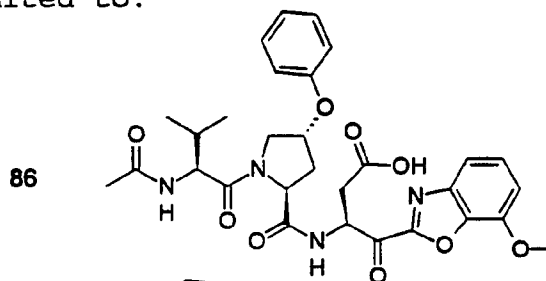


;

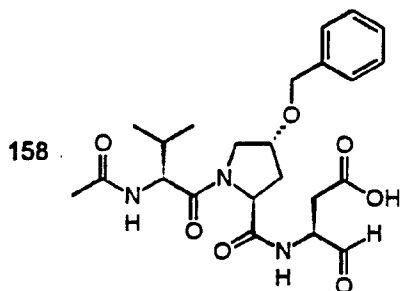
- 83 -

When R₁ is:

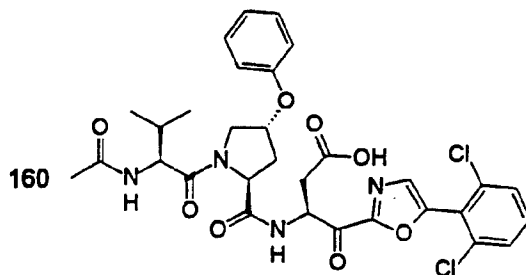
preferred compounds of this invention include but are not limited to:



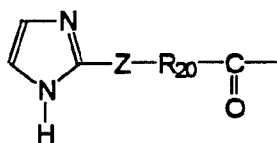
- 84 -



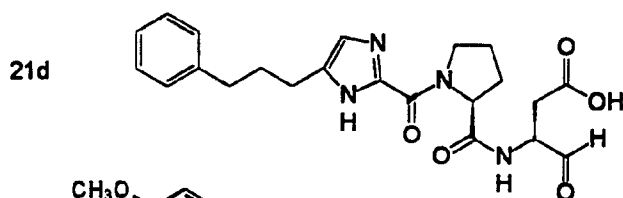
; and

When R_1 is:

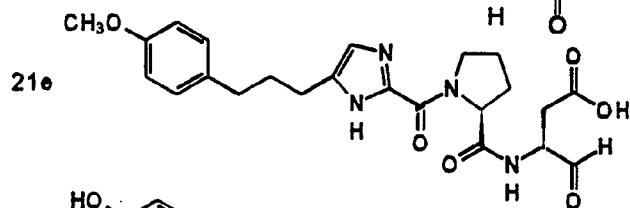
(g2)



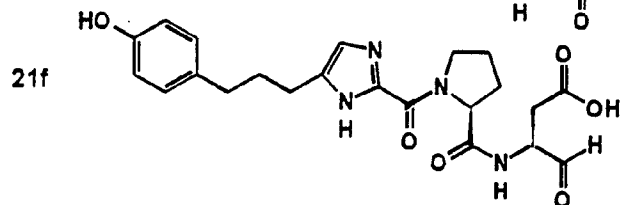
15 preferred compounds of this invention include but are
not limited to:



;

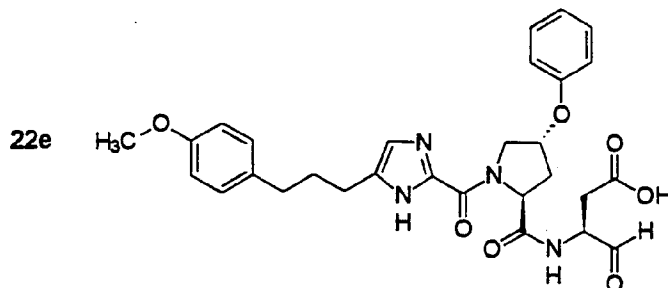


;

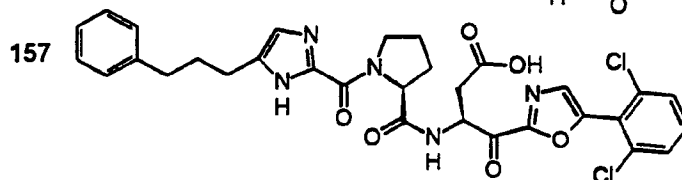


;

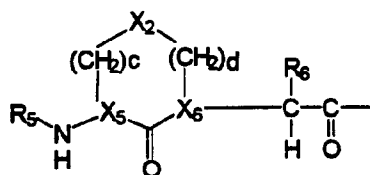
- 85 -



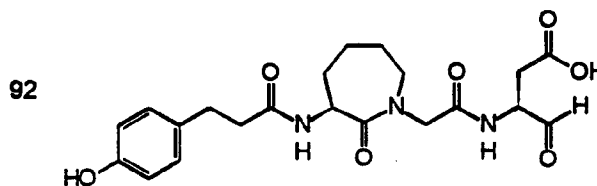
; and

When R_1 is:

(o)



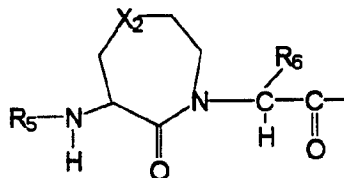
preferred compounds of this invention include but are not limited to:



A preferred compound of embodiment B of this invention employs formula α , wherein:

 R_1 is:

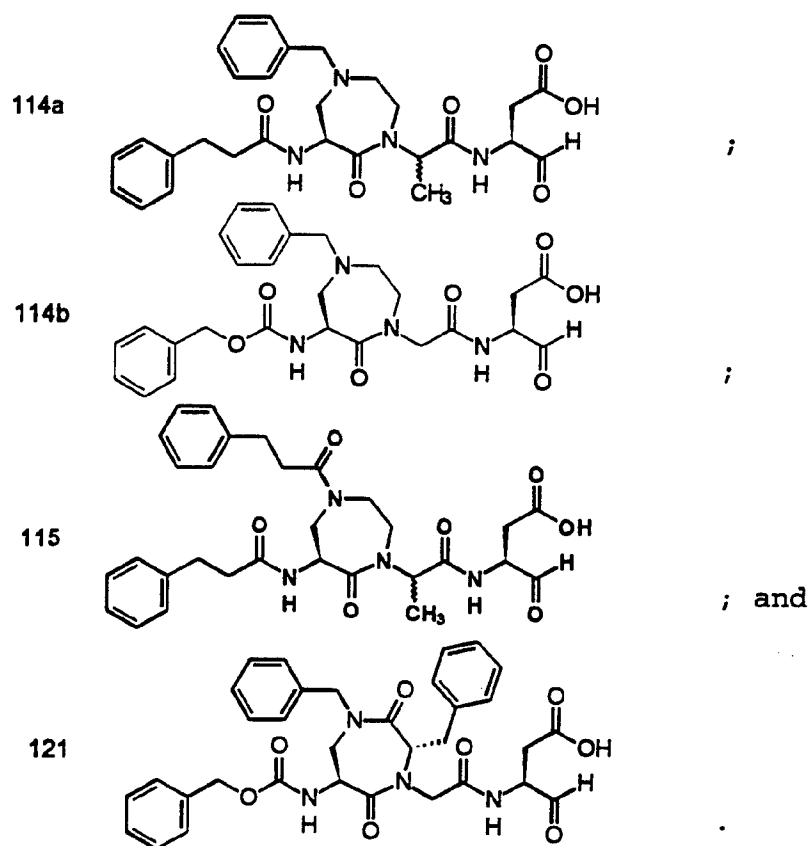
(o6)

 X_2 is -NH-;

- 86 -

m is 1;
 T is $-\text{CO}_2\text{H}$;
 R_3 is $-\text{CO}-\text{R}_{13}$.

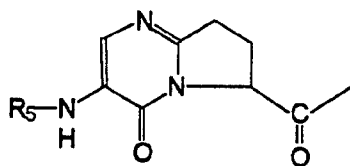
Preferred compounds of this embodiment
 5 include but are not limited to:



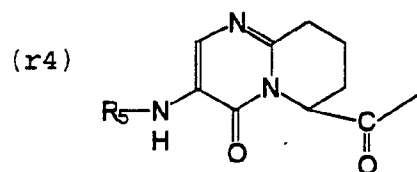
When R_1 is:

15

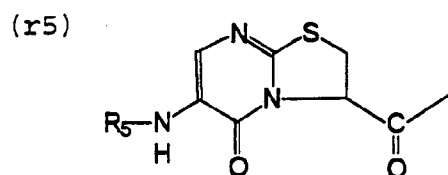
(r3)



- 87 -

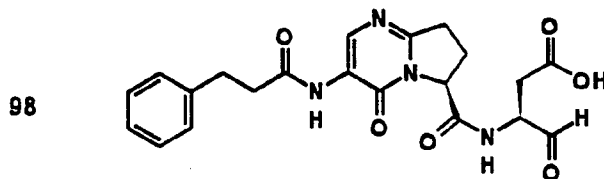


; or

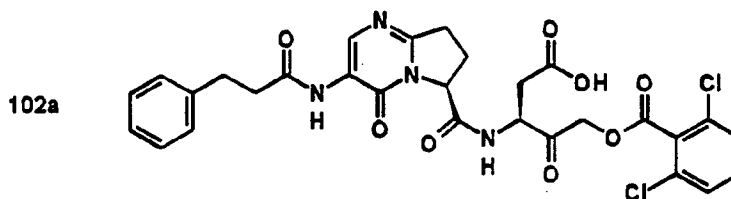


5 optionally substituted with Q₁;

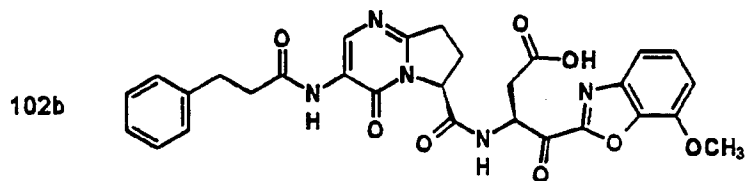
preferred compounds of embodiment B of this invention
include but are not limited to:



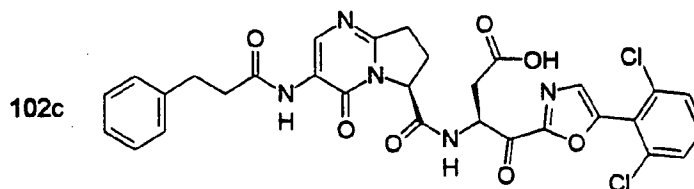
;



;



; and

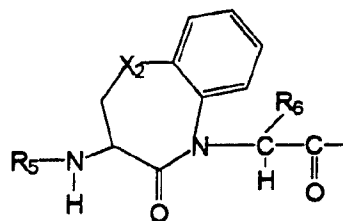


15

- 88 -

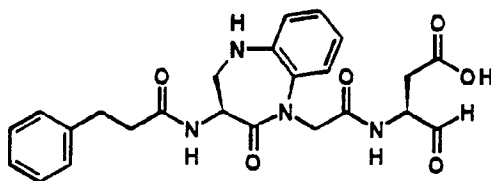
When R₁ is:

(w1)



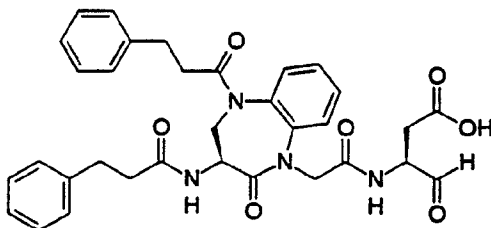
5 preferred compounds of this invention include but are not limited to:

106a



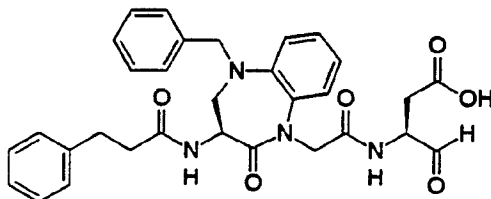
10

106b



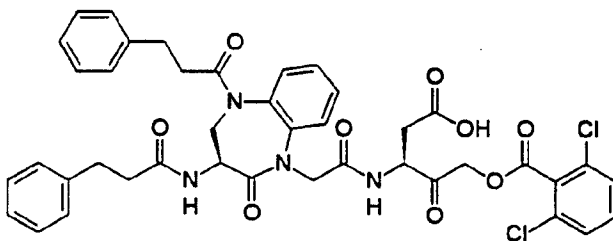
15

106c

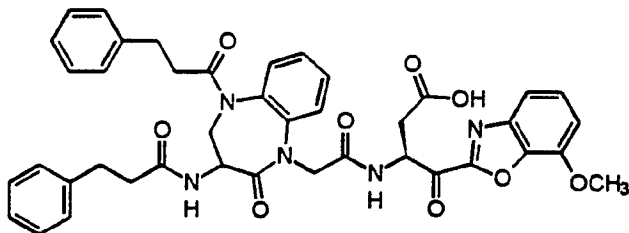


20

108a



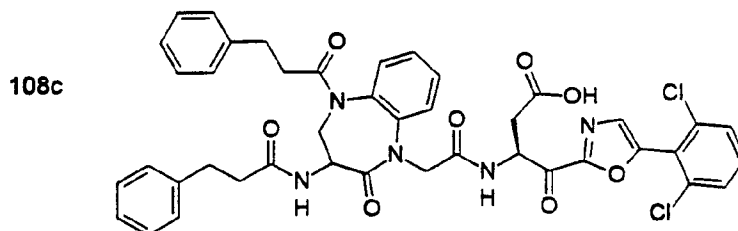
108b



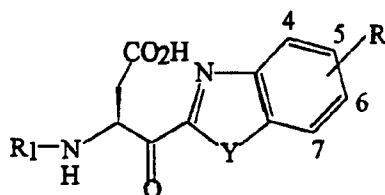
25

; and

- 89 -



The ICE inhibitors of another embodiment (C) of this invention are represented by the formula α :



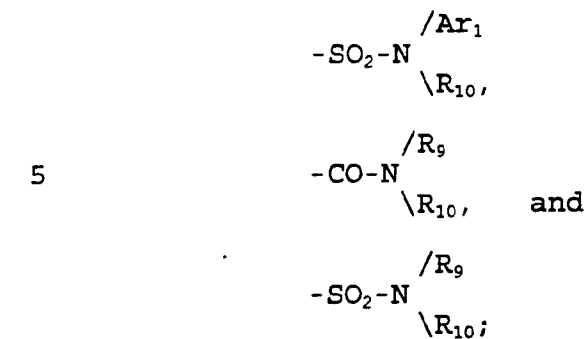
wherein the ring is optionally substituted with one or more R groups, preferably 0, 1 or 2; and wherein:

R_1 is $R_5-(A)_p-$;

R_5 is selected from the group consisting of:

- H,
- Ar₁,
- CO-Ar₁,
- SO₂-Ar₁,
- R₉,
- CO-R₉,
- CO-O-R₉,
- SO₂-R₉,
- /Ar₁
- CO-N
- \R₁₀,

- 90 -



each A is independently selected from the group
consisting of any α -amino acid;

p is 0, 1, 2, 3 or 4;

Y is:

15 -O-,
 -S- or
 -NH;

R is:

20 -H,
 -O-C₁₋₆ alkyl,
 -NH(C₁₋₆ alkyl),
 -N(C₁₋₆ alkyl)₂,
 -S-C₁₋₆ alkyl,
 -C₁₋₆ alkyl, or
25 -Q₂;

each R₉ is a C₁₋₆ straight or branched alkyl group
optionally singly or multiply substituted by -OH, -F,
or =O and optionally substituted with one or two Ar₁
groups;

30 each R₁₀ is independently selected from the group
consisting of -H or a C₁₋₆ straight or branched alkyl
group;

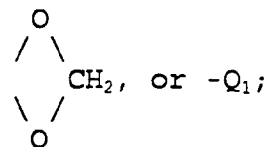
- 91 -

each T_1 is independently selected from the group consisting of:

- CH=CH-,
- O-,
- 5 -S-,
- SO-,
- SO₂-,
- NR₁₀-,
- NR₁₀-CO-,
- 10 -CO-,
- O-CO-,
- CO-O-,
- CO-NR₁₀-,
- O-CO-NR₁₀-,
- 15 -NR₁₀-CO-O-,
- NR₁₀-CO-NR₁₀-,
- SO₂-NR₁₀-,
- NR₁₀-SO₂-, and
- NR₁₀-SO₂-NR₁₀-,

- 20 each Ar_1 is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said
- 25 cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle
- 30 group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by: -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂,

- 92 -

-CN, =O, -OH, -perfluoro C₁₋₃ alkyl,

5

each Q₁ is independently selected from the group consisting of:

-Ar₁-R₉,

10

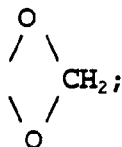
-T₁-R₉,

and

- (CH₂)_{1,2,3}-T₁-R₉;

each Q₂ is independently selected from the group consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂,

15

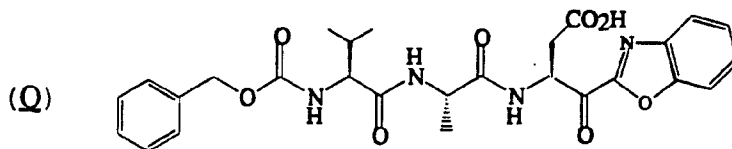
-CN, -CF₃, and

20

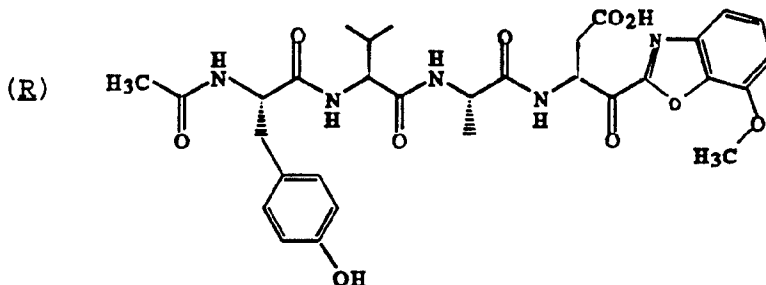
provided that when -Ar₁ is substituted with a Q₁ group which comprises one or more additional -Ar₁ groups, said additional -Ar₁ groups are not substituted with Q₁.

25

Preferred compounds of embodiment C of this invention include but are not limited to:

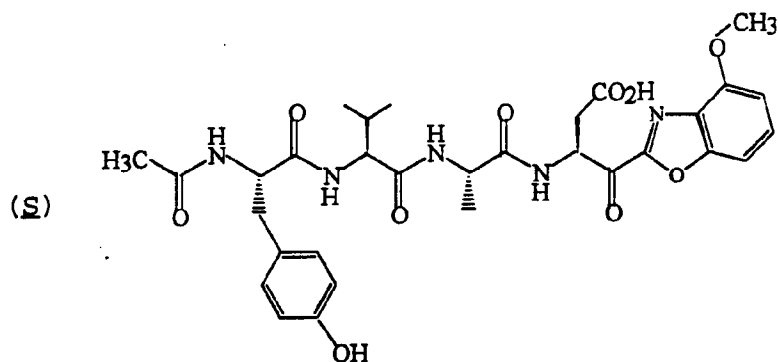


;

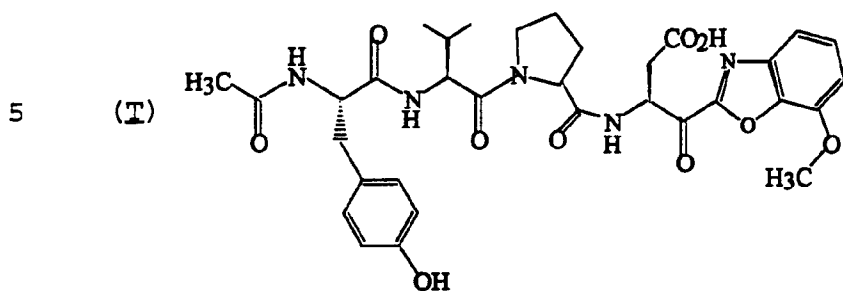


;

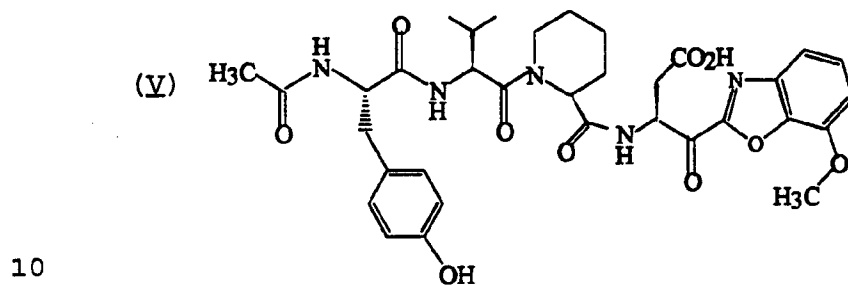
- 93 -



;



; and



Preferred compounds of embodiment C of this invention are also those in which each A is independently selected from the group consisting of the

15 α -amino acids:

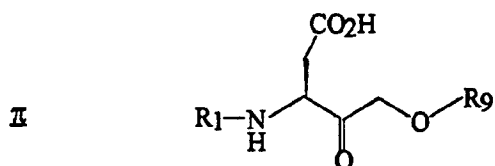
alanine,
 histidine,
 lysine,
 phenylalanine,
 20 proline,
 tyrosine,
 valine,

- 94 -

leucine,
 isoleucine,
 glutamine,
 methionine,
 5 homoproline,
 3-(2-thienyl) alanine, and
 3-(3-thienyl) alanine.

The ICE inhibitors of another embodiment (D)
 of this invention are represented by the formula II:

10



wherein:

R_1 is $R_5-(A)_p-$;

each T_1 is independently selected from the group
 15 consisting of:

-CH=CH-,
 -O-,
 -S-,
 -SO-,
 20 -SO₂-,
 -NR₁₀-,
 -NR₁₀-CO-,
 -CO-,
 -O-CO-,
 25 -CO-O-,
 -CO-NR₁₀-,
 -O-CO-NR₁₀-,
 -NR₁₀-CO-O-,

- 95 -

$\text{-NR}_{10}\text{-CO-NR}_{10}\text{-}$,
 $\text{-SO}_2\text{-NR}_{10}\text{-}$,
 $\text{-NR}_{10}\text{-SO}_2\text{-}$, and
 $\text{-NR}_{10}\text{-SO}_2\text{-NR}_{10}\text{-}$;

5 R_5 is selected from the group consisting of:
 -H ,
 -Ar_1 ,
 -CO-Ar_1 ,
 $\text{-SO}_2\text{-Ar}_1$,
 10 -R_9 ,
 -CO-R_9 ,
 -CO-O-R_9 ,
 $\text{-SO}_2\text{-R}_9$,
 $\text{-CO-N} \begin{matrix} / \text{Ar}_1 \\ \backslash \text{R}_{10} \end{matrix}$,
 15 $\text{-SO}_2\text{-N} \begin{matrix} / \text{Ar}_1 \\ \backslash \text{R}_{10} \end{matrix}$,
 $\text{-CO-N} \begin{matrix} / \text{R}_9 \\ \backslash \text{R}_{10} \end{matrix}$, and
 $\text{-SO}_2\text{-N} \begin{matrix} / \text{R}_9 \\ \backslash \text{R}_{10} \end{matrix}$;

each A is independently selected from the group consisting of any α -amino acid;

p is 0, 1, 2, 3 or 4;

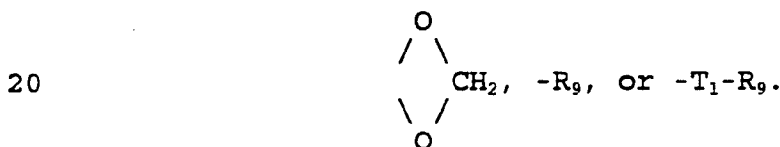
30 each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted by -OH , -F , or $=\text{O}$ and optionally substituted with an Ar_1 group;

each R_{10} is independently selected from the group

- 96 -

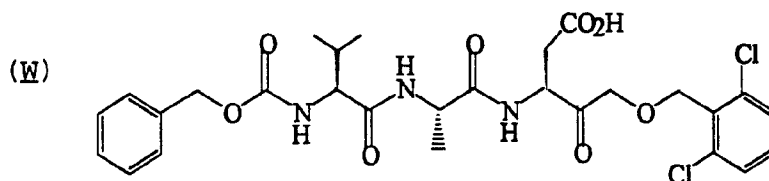
consisting of -H or a C₁₋₆ straight or branched alkyl group;

Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6,
 5 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1
 10 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings,
 15 and said cyclic group optionally being singly or multiply substituted by -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CH₃, =O, -OH, -perfluoro C₁₋₃ alkyl, or

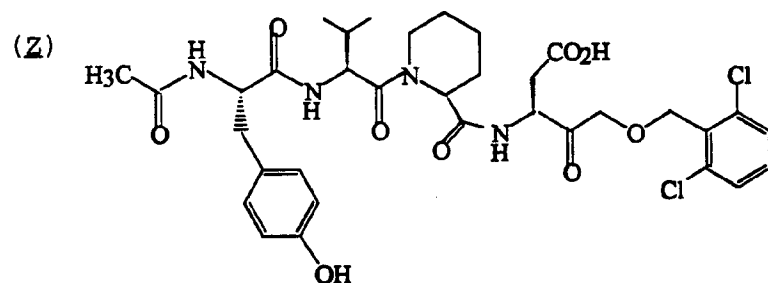
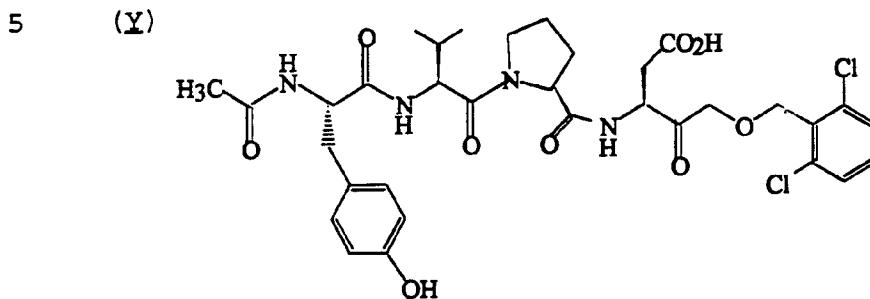
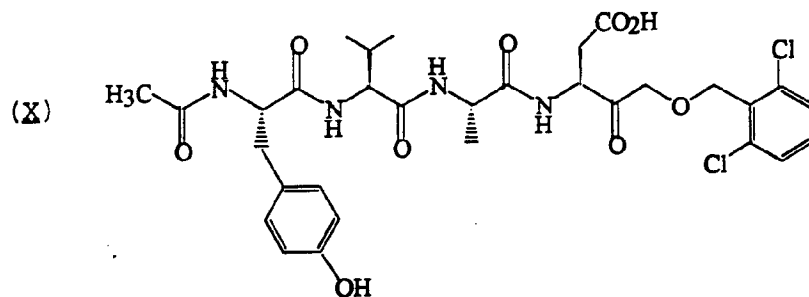


Preferred compounds of embodiment D of this invention are those in which R₉ is a C₁₋₄ straight or
 25 branched alkyl substituted with Ar₁ when Ar₁ is phenyl.

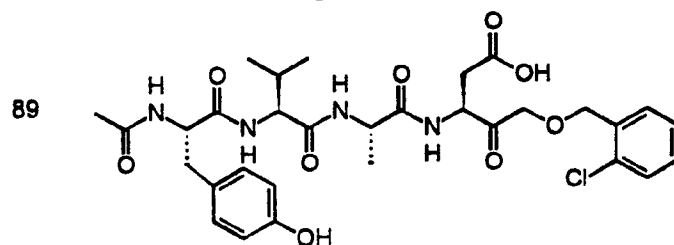
Preferred compounds of embodiment D of this invention include but are not limited to:



- 97 -



; and



10

Preferred compounds of embodiment D of this invention are also those in which A is independently selected from the group consisting of the α -amino acids:

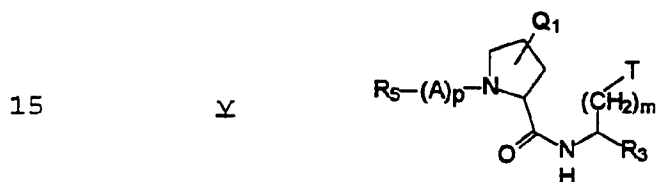
15

alanine,
histidine,

- 98 -

lysine,
 phenylalanine,
 proline,
 tyrosine,
 5 valine,
 leucine,
 isoleucine,
 glutamine,
 methionine,
 10 homoproline,
 3-(2-thienyl) alanine, and
 3-(3-thienyl) alanine.

The ICE inhibitors of another embodiment (E)
 of this invention are represented by formula γ :



wherein:

m is 0, 1, or 2;

20 T is $-\text{CO}_2\text{H}$, or any bioisosteric
 replacement for $-\text{CO}_2\text{H}$,

R₃ is
 -CN,
 -COR₁₃, or
 25 -COCO-N $\begin{matrix} /R_5 \\ \backslash R_{10} \end{matrix}$

R₅ is selected from the group consisting of:

- 99 -

- H,
 -Ar₁,
 -CO-Ar₁,
 -SO₂-Ar₁,
 5 -R₉,
 -CO-R₉,
 -CO-O-R₉,
 -SO₂-R₉,
 10 -CO-N $\begin{matrix} /Ar_1 \\ \backslash R_{10} \end{matrix}$,
 -SO₂-N $\begin{matrix} /Ar_1 \\ \backslash R_{10} \end{matrix}$,
 15 -CO-N $\begin{matrix} /R_9 \\ \backslash R_{10} \end{matrix}$, and
 20 -SO₂-N $\begin{matrix} /R_9 \\ \backslash R_{10} \end{matrix}$;

each A is independently selected from the group consisting of any α-amino acid;

p is 2 or 3;

- 25 each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one Ar₁ group;

each T₁ is independently selected from the group consisting of:

- 30 -CH=CH-,
 -O-,
 -S-,
 -SO-,

- 100 -

-SO₂-,
 -NR₁₀-,
 -NR₁₀-CO-,
 -CO-,
 5 -O-CO-,
 -CO-O-,
 -CO-NR₁₀-,
 -O-CO-NR₁₀-,
 -NR₁₀-CO-O-,
 10 -NR₁₀-CO-NR₁₀-,
 -SO₂-NR₁₀-,
 -NR₁₀-SO₂-, and
 -NR₁₀-SO₂-NR₁₀-;

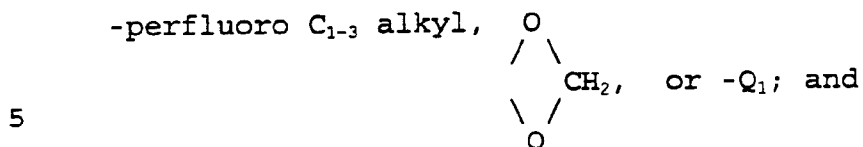
15 each R₁₀ is independently selected from the group
 consisting of -H or a -C₁₋₆ straight or branched alkyl
 group;

 each R₁₃ is independently selected from the group
 consisting of H, R₉, Ar₂, and CH₂T₁R₉;

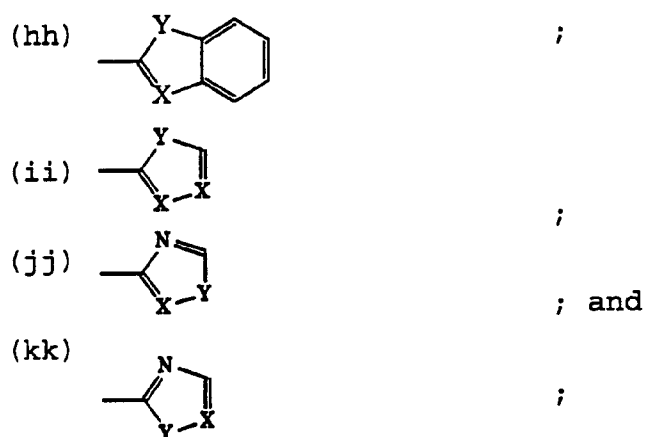
20 each Ar₁ is a cyclic group independently selected
 from the set consisting of an aryl group which contains
 6, 10, 12, or 14 carbon atoms and between 1 and 3
 rings, a cycloalkyl group which contains between 3 and
 15 carbon atoms and between 1 and 3 rings, said
 25 cycloalkyl group being optionally benzofused, and a
 heterocycle group containing between 5 and 15 ring
 atoms and between 1 and 3 rings, said heterocycle group
 containing at least one heteroatom group selected from
 -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle
 30 group optionally containing one or more double bonds,
 said heterocycle group optionally comprising one or
 more aromatic rings, and said cyclic group optionally
 being singly or multiply substituted by -NH₂, -CO₂H,

- 101 -

-Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH,
 -perfluoro C₁₋₃ alkyl,



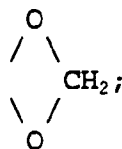
each Ar₂ is independently selected from the
 following group, in which any ring may optionally be
 10 singly or multiply substituted by -Q₁ and -Q₂:



each Q₁ is independently selected from the group
 20 consisting of:

-Ar₁
 -O-Ar₁
 -R₉,
 -T₁-R₉, and
 25 -(CH₂)_{1,2,3}-T₁-R₉;

each Q₂ is independently selected from the group
 consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I,
 30 -NO₂, -CN, -CF₃, and

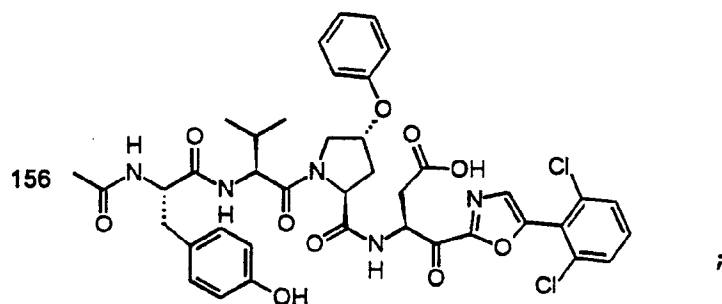
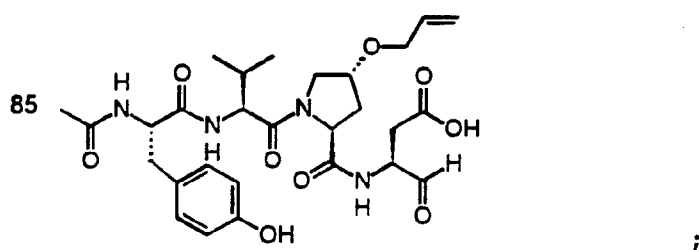
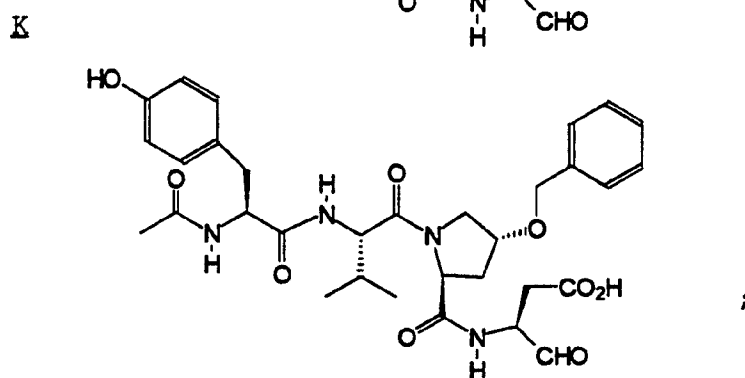
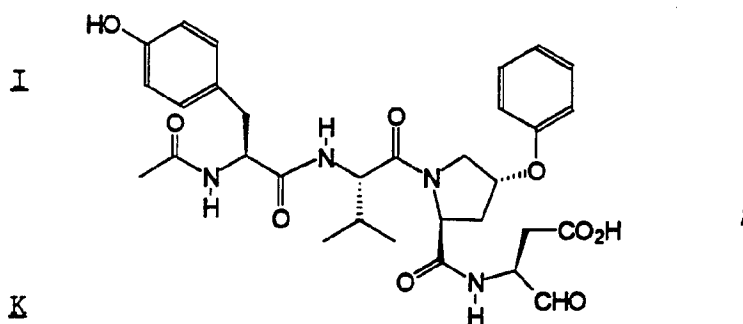


35 provided that when -Ar₁ is substituted with a Q₁

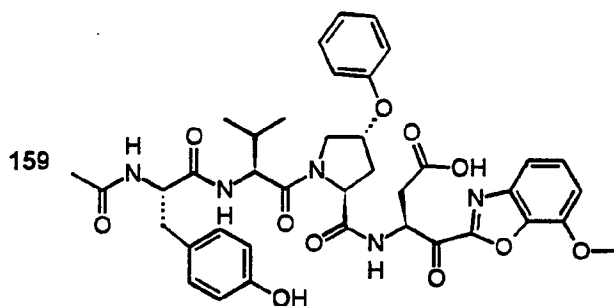
- 102 -

group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1 .

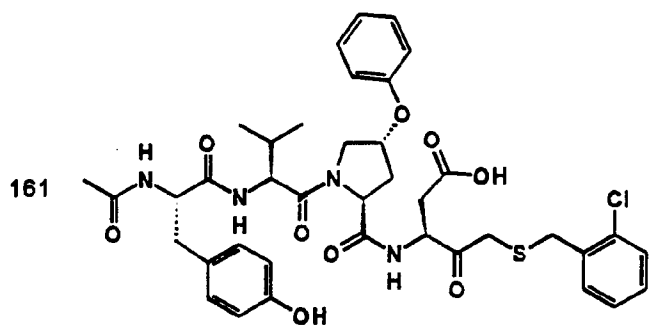
Preferred compounds of embodiment E of this
5 invention include but are not limited to:



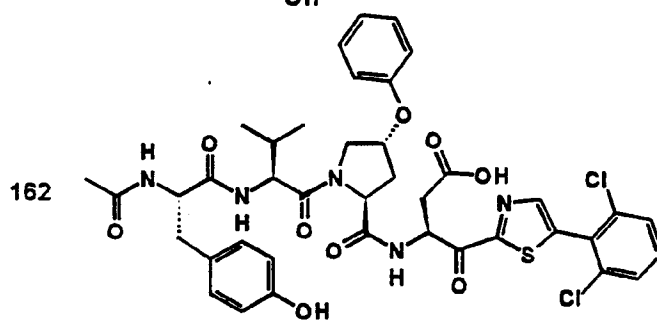
- 103 -



;



; and



5

Preferred compounds of embodiment E of this invention are also those in which A is independently selected from the group consisting the α -amino acids:

10

alanine,
 histidine,
 lysine,
 phenylalanine,
 proline,
 tyrosine,
 valine,
 leucine,

15

- 104 -

isoleucine,
 glutamine,
 methionine,
 homoproline,
 5 3-(2-thienyl) alanine, and
 3-(3-thienyl) alanine.

The ICE inhibitors of another embodiment (F)
 of this invention are represented by formula δ :



10 wherein:

R_1 is $\text{R}_5-(\text{A})_p-$;

R_5 is selected from the group consisting of:

-H,
 - Ar_1 ,
 15 -CO- Ar_1 ,
 -SO₂- Ar_1 ,
 - R_9 ,
 -CO- R_9 ,
 -CO-O- R_9 ,
 20 -SO₂- R_9 ,
 -CO-N $\begin{array}{l} / \text{Ar}_1 \\ \backslash \text{R}_{10} \end{array}$,
 25 -SO₂-N $\begin{array}{l} / \text{Ar}_1 \\ \backslash \text{R}_{10} \end{array}$,
 -CO-N $\begin{array}{l} / \text{R}_9 \\ \backslash \text{R}_{10} \end{array}$, and
 30 -SO₂-N $\begin{array}{l} / \text{R}_9 \\ \backslash \text{R}_{10} \end{array}$;

- 105 -

each A is independently selected from the group consisting of any α -amino acid;

p is 0, 1, 2, 3 or 4;

5 each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one Ar₁ group;

each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

10 each T₁ is independently selected from the group consisting of:

-CH=CH-,

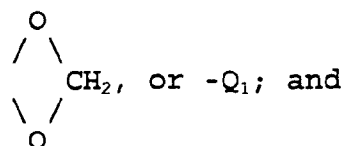
-O-,

-S-,

15 -SO-,

each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 20 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from 25 -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -NH₂, -CO₂H, 30 -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH,

- 106 -

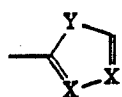
-perfluoro C₁₋₃ alkyl,

5

each Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ and -Q₂:

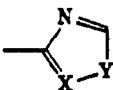
10

(ii)



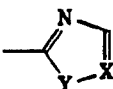
;

(jj)



; and

(kk)



;

15

each Q₁ is independently selected from the group consisting of:

-Ar₁-O-Ar₁

20

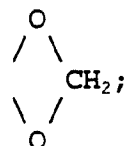
-R₉,-T₁-R₉,

and

-(CH₂)_{1,2,3}-T₁-R₉;

each Q₂ is independently selected from the group consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN, -CF₃, and

25



30

provided that when -Ar₁ is substituted with a Q₁ group which comprises one or more additional -Ar₁

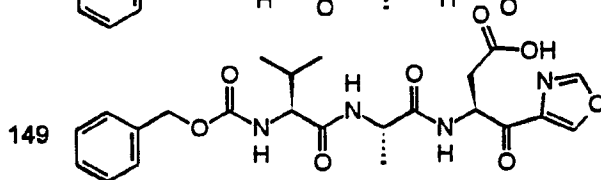
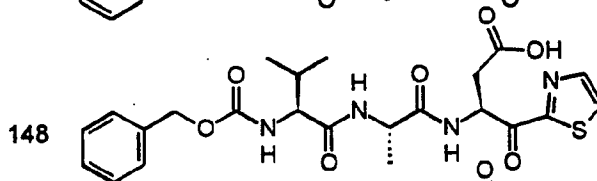
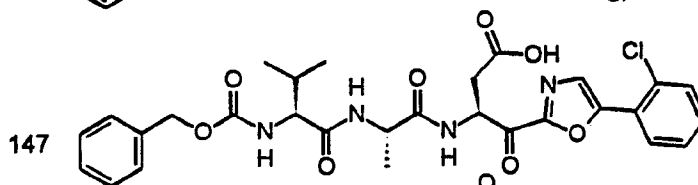
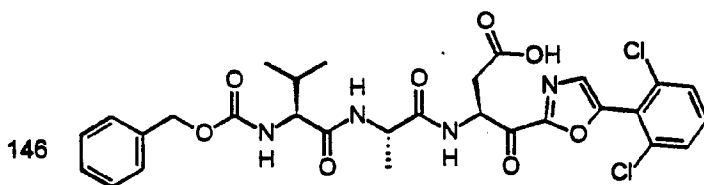
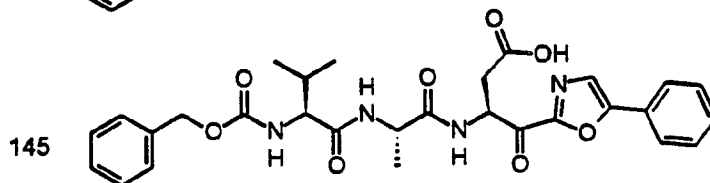
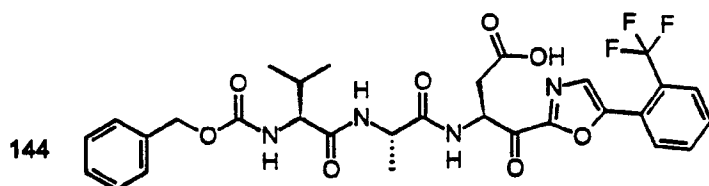
- 107 -

groups, said additional $-\text{Ar}_1$ groups are not substituted with Q_1 ;

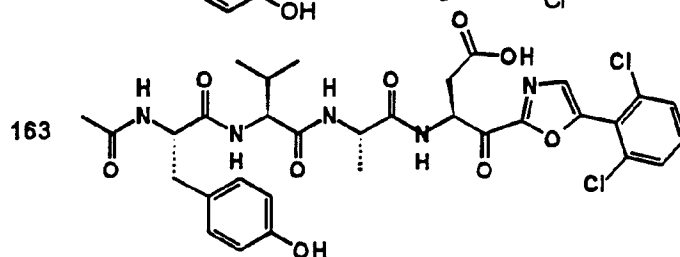
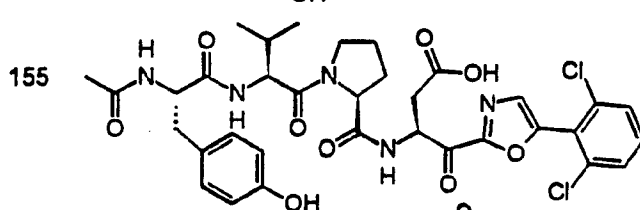
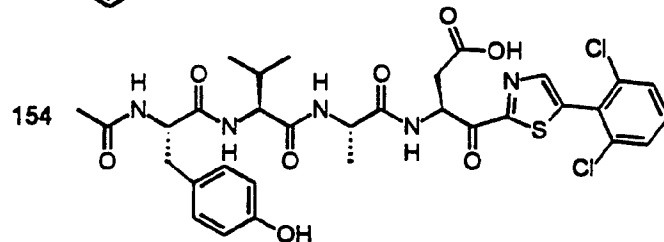
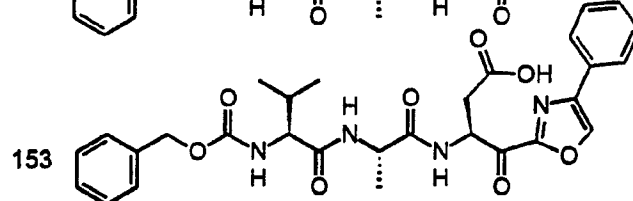
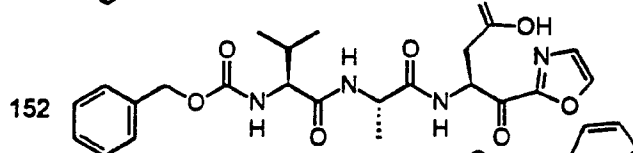
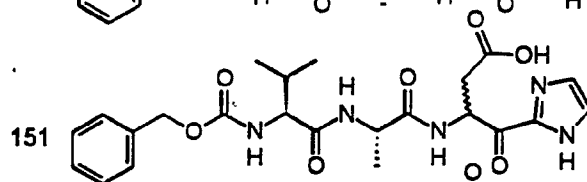
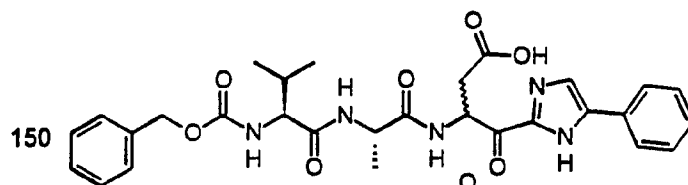
each X is independently selected from the group consisting of $=\text{N}-$, and $=\text{CH}-$; and

5 each Y is independently selected from the group consisting of $-\text{O}-$, $-\text{S}-$, and $-\text{NH}$.

Preferred compounds of embodiment F of this invention include but are not limited to:



- 108 -



Preferred compounds of embodiment F of this invention are also those in which A is independently selected from the group consisting the α -amino acids: alanine,

- 109 -

histidine,
lysine,
phenylalanine,
proline,
5 tyrosine,
valine,
leucine,
isoleucine,
glutamine,
10 methionine,
homoproline,
3-(2-thienyl) alanine, and
3-(3-thienyl) alanine.

The compounds of this invention having a
15 molecular weight of less than or equal to about 700
Daltons, and more preferably between about 400 and 600
Daltons, are preferred. These preferred compounds may
be readily absorbed by the bloodstream of patients upon
oral administration. This oral availability makes such
20 compounds excellent agents for orally-administered
treatment and prevention regimens against IL-1 mediated
diseases.

The ICE inhibitors of this invention may be
synthesized using conventional techniques.
25 Advantageously, these compounds are conveniently
synthesized from readily available starting materials.

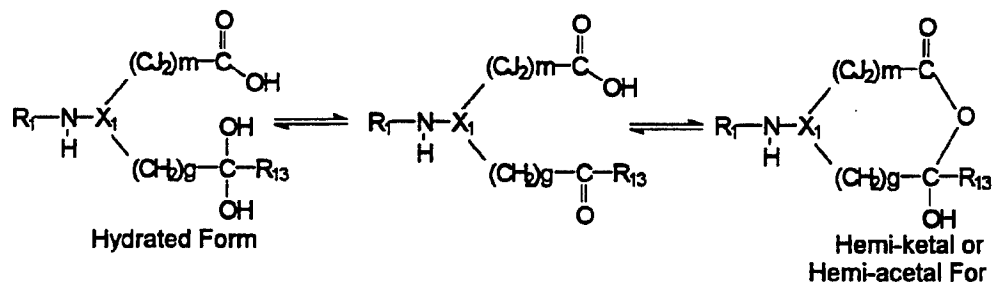
The compounds of this invention are among the
most readily synthesized ICE inhibitors known.
Previously described ICE inhibitors often contain four
30 or more chiral centers and numerous peptide linkages.
The relative ease with which the compounds of this
invention can be synthesized represents an enormous
advantage in the large scale production of these

- 110 -

compounds.

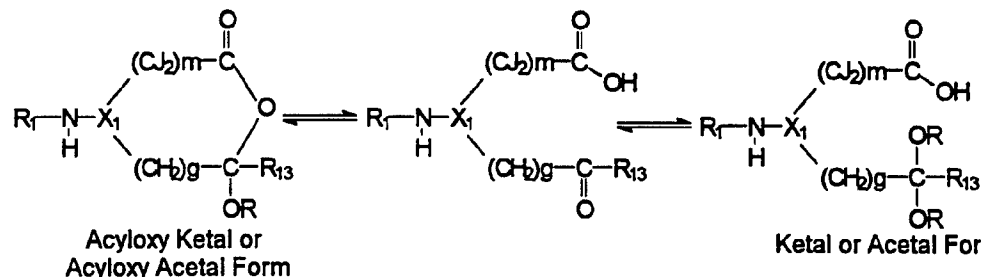
It should be understood that the compounds of this invention may exist in various equilibrium forms, depending on conditions including choice of solvent, pH, and others known to the practitioner skilled in the art. All such forms of these compounds are expressly included in the present invention. In particular, many of the compounds of this invention, especially those which contain aldehyde or ketone groups in R₃ and carboxylic acid groups in T, may take hemi-ketal (or hemi-acetal) or hydrated forms, as depicted below:

(EQ1)



Depending on the choice of solvent and other conditions known to the practitioner skilled in the art, compounds of this invention may also take acyloxy ketal, acyloxy acetal, ketal or acetal form:

(EQ2)



In addition, it should be understood that the equilibrium forms of the compounds of this invention may include tautomeric forms. All such forms of these

- 111 -

compounds are expressly included in the present invention.

It should be understood that the compounds of this invention may be modified by appropriate functionalities to enhance selective biological properties. Such modifications are known in the art and include those which increase biological penetration into a given biological system (e.g., blood, lymphatic system, central nervous system), increase oral availability, increase solubility to allow administration by injection, alter metabolism and alter rate of excretion. In addition, the compounds may be altered to pro-drug form such that the desired compound is created in the body of the patient as the result of the action of metabolic or other biochemical processes on the pro-drug. Some examples of pro-drug forms include ketal, acetal, oxime, and hydrazone forms of compounds which contain ketone or aldehyde groups, especially where they occur in the R₃ group of the compounds of this invention.

The compounds of this invention are excellent ligands for ICE. Accordingly, these compounds are capable of targeting and inhibiting events in IL-1 mediated diseases, such as the conversion of precursor IL-1 β to mature IL-1 β and, thus, the ultimate activity of that protein in inflammatory diseases, autoimmune diseases and neurodegenerative diseases. For example, the compounds of this invention inhibit the conversion of precursor IL-1 β to mature IL-1 β by inhibiting ICE. Because ICE is essential for the production of mature IL-1, inhibition of that enzyme effectively blocks initiation of IL-1 mediated physiological effects and symptoms, such as inflammation, by inhibiting the production of mature IL-1. Thus, by inhibiting IL-1 β precursor activity, the compounds of this invention

- 112 -

effectively function as IL-1 inhibitors.

The compounds of this invention may be employed in a conventional manner for the treatment of diseases which are mediated by IL-1. Such methods of treatment, their dosage levels and requirements may be
5 selected by those of ordinary skill in the art from available methods and techniques. For example, a compound of this invention may be combined with a pharmaceutically acceptable adjuvant for administration
10 to a patient suffering from an IL-1 mediated disease in a pharmaceutically acceptable manner and in an amount effective to lessen the severity of that disease.

Alternatively, the compounds of this invention may be used in compositions and methods for
15 treating or protecting individuals against IL-1 mediated diseases over extended periods of time. The compounds may be employed in such compositions either alone or together with other compounds of this invention in a manner consistent with the conventional
20 utilization of ICE inhibitors in pharmaceutical compositions. For example, a compound of this invention may be combined with pharmaceutically acceptable adjuvants conventionally employed in vaccines and administered in prophylactically effective
25 amounts to protect individuals over an extended period time against IL-1 mediated diseases.

The compounds of this invention may also be co-administered with other ICE inhibitors to increase the effect of therapy or prophylaxis against various
30 IL-1-mediated diseases.

In addition, the compounds of this invention may be used in combination either conventional anti-inflammatory agents or with matrix metalloprotease inhibitors, lipxygenase inhibitors and antagonists of
35 cytokines other than IL-1 β .

- 113 -

The compounds of this invention can also be administered in combination with immunomodulators (e.g., bropirimine, anti-human alpha interferon antibody, IL-2, GM-CSF, methionine enkephalin, 5 interferon alpha, diethyldithiocarbamate, tumor necrosis factor, naltrexone and rEPO) or with prostaglandins, to prevent or combat IL-1-mediated disease symptoms such as inflammation.

When the compounds of this invention are 10 administered in combination therapies with other agents, they may be administered sequentially or concurrently to the patient. Alternatively, pharmaceutical or prophylactic compositions according to this invention may be comprised of a combination of 15 an ICE inhibitor of this invention and another therapeutic or prophylactic agent.

Pharmaceutical compositions of this invention comprise any of the compounds of the present invention, and pharmaceutically acceptable salts thereof, with any 20 pharmaceutically acceptable carrier, adjuvant or vehicle. Pharmaceutically acceptable carriers, adjuvants and vehicles that may be used in the pharmaceutical compositions of this invention include, but are not limited to, ion exchangers, alumina, 25 aluminum stearate, lecithin, serum proteins, such as human serum albumin, buffer substances such as phosphates, glycine, sorbic acid, potassium sorbate, partial glyceride mixtures of saturated vegetable fatty acids, water, salts or electrolytes, such as protamine 30 sulfate, disodium hydrogen phosphate, potassium hydrogen phosphate, sodium chloride, zinc salts, colloidal silica, magnesium trisilicate, polyvinyl pyrrolidone, cellulose-based substances, polyethylene glycol, sodium carboxymethylcellulose, polyacrylates, 35 waxes, polyethylene-polyoxypropylene-block polymers,

- 114 -

polyethylene glycol and wool fat.

The pharmaceutical compositions of this invention may be administered orally, parenterally, by inhalation spray, topically, rectally, nasally, buccally, vaginally or via an implanted reservoir. We prefer oral administration. The pharmaceutical compositions of this invention may contain any conventional non-toxic pharmaceutically-acceptable carriers, adjuvants or vehicles. The term parenteral as used herein includes subcutaneous, intracutaneous, intravenous, intramuscular, intra-articular, intrasynovial, intrasternal, intrathecal, intralesional and intracranial injection or infusion techniques.

The pharmaceutical compositions may be in the form of a sterile injectable preparation, for example, as a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to techniques known in the art using suitable dispersing or wetting agents (such as, for example, Tween 80) and suspending agents. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are mannitol, water, Ringer's solution and isotonic sodium chloride solution. In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose, any bland fixed oil may be employed including synthetic mono- or diglycerides. Fatty acids, such as oleic acid and its glyceride derivatives are useful in the preparation of injectables, as are natural pharmaceutically-acceptable oils, such as olive oil or castor oil, especially in their polyoxyethylated versions. These oil solutions

- 115 -

or suspensions may also contain a long-chain alcohol diluent or dispersant such as Ph. Hely or a similar alcohol.

5 The pharmaceutical compositions of this invention may be orally administered in any orally acceptable dosage form including, but not limited to, capsules, tablets, and aqueous suspensions and solutions. In the case of tablets for oral use,
10 carriers which are commonly used include lactose and corn starch. Lubricating agents, such as magnesium stearate, are also typically added. For oral administration in a capsule form, useful diluents include lactose and dried corn starch. When aqueous
15 suspensions are administered orally, the active ingredient is combined with emulsifying and suspending agents. If desired, certain sweetening and/or flavoring and/or coloring agents may be added.

 The pharmaceutical compositions of this
20 invention may also be administered in the form of suppositories for rectal administration. These compositions can be prepared by mixing a compound of this invention with a suitable non-irritating excipient which is solid at room temperature but liquid at the
25 rectal temperature and therefore will melt in the rectum to release the active components. Such materials include, but are not limited to, cocoa butter, beeswax and polyethylene glycols.

 Topical administration of the pharmaceutical
30 compositions of this invention is especially useful when the desired treatment involves areas or organs readily accessible by topical application. For application topically to the skin, the pharmaceutical composition should be formulated with a suitable
35 ointment containing the active components suspended or

- 116 -

dissolved in a carrier. Carriers for topical administration of the compounds of this invention include, but are not limited to, mineral oil, liquid petroleum, white petroleum, propylene glycol, polyoxy-
5 ethylene polyoxypropylene compound, emulsifying wax and water. Alternatively, the pharmaceutical composition can be formulated with a suitable lotion or cream containing the active compound suspended or dissolved in a carrier. Suitable carriers include, but are not
10 limited to, mineral oil, sorbitan monostearate, polysorbate 60, cetyl esters wax, cetearyl alcohol, 2-octyldodecanol, benzyl alcohol and water. The pharmaceutical compositions of this invention may also be topically applied to the lower intestinal tract by
15 rectal suppository formulation or in a suitable enema formulation. Topically-transdermal patches are also included in this invention.

The pharmaceutical compositions of this invention may be administered by nasal aerosol or
20 inhalation. Such compositions are prepared according to techniques well-known in the art of pharmaceutical formulation and may be prepared as solutions in saline, employing benzyl alcohol or other suitable preservatives, absorption promoters to enhance
25 bioavailability, fluorocarbons, and/or other solubilizing or dispersing agents known in the art.

The IL-1 mediated diseases which may be treated or prevented by the compounds of this invention include, but are not limited to, inflammatory diseases,
30 autoimmune diseases and neurodegenerative diseases.

Inflammatory diseases which may be treated or prevented include, for example, septic shock, septicemia, and adult respiratory distress syndrome. Target autoimmune diseases include, for example,
35 rheumatoid, arthritis, systemic lupus erythematosus,

- 117 -

scleroderma, chronic thyroiditis, Graves' disease, autoimmune gastritis, insulin-dependent diabetes mellitus, autoimmune hemolytic anemia, autoimmune neutropenia, thrombocytopenia, chronic active hepatitis, myasthenia gravis and multiple sclerosis. And target neurodegenerative diseases include, for example, amyotrophic lateral sclerosis, Alzheimer's disease, Parkinson's disease, and primary lateral sclerosis. The ICE inhibitors of this invention may also be used to promote wound healing. And the ICE inhibitors of this invention may be used to treat infectious diseases.

Although this invention focuses on the use of the compounds disclosed herein for preventing and treating IL-1-mediated diseases, the compounds of this invention can also be used as inhibitory agents for other cysteine proteases.

The compounds of this invention are also useful as commercial reagents which effectively bind to ICE or other cysteine proteases. As commercial reagents, the compounds of this invention, and their derivatives, may be used to block proteolysis of a target peptide or may be derivatized to bind to a stable resin as a tethered substrate for affinity chromatography applications. These and other uses which characterize commercial cysteine protease inhibitors will be evident to those of ordinary skill in the art.

In order that this invention be more fully understood, the following examples are set forth. These examples are for the purpose of illustration only and are not to be construed as limiting the scope of the invention in any way.

- 118 -

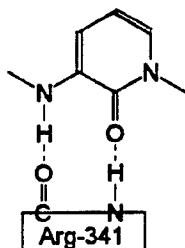
Example 1

The following example demonstrates a process of drug design which embodies the present invention:

5 Step 1) Pick 2 hydrogen bonding moieties of ICE, here, the backbone C=O and N-H of Arg-341.

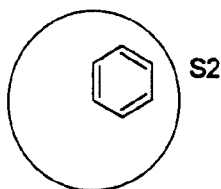
10 Step 2) Pick a scaffold, here, a pyridone derivative, and confirm that the hydrogen bonding moieties of the scaffold are capable of forming satisfactory hydrogen bonds with the hydrogen bonding moieties selected in step 1. This confirmation is performed by using molecular mechanics techniques to minimize the scaffold fragment in the context of the active site of ICE.

(Z1)



15 Step 3) Pick a hydrophobic pocket, here, S2, as next target and a hydrophobic moiety, here, benzene. Minimize the benzene group within the S2 pocket to assure that substantial hydrophobic overlap is obtained.

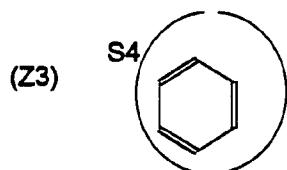
(Z2)



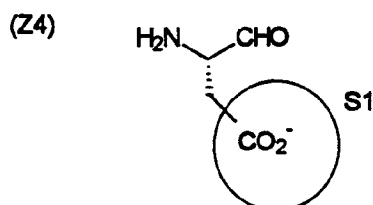
20 Step 4) Pick another hydrophobic pocket, here, S4, as the next target and a hydrophobic moiety,

- 119 -

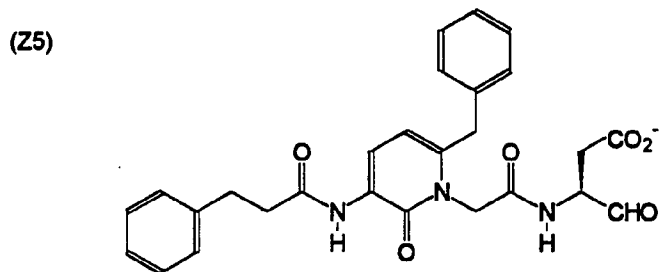
here, benzene. Minimize the benzene group within the S4 pocket to ensure that substantial hydrophobic overlap is obtained.



5 Step 5) Fill the S1 polar pocket with an electronegative moiety, here, a carboxylate sidechain provided by aspartic acid in which the C-terminus has been reduced to an aldehyde. Minimize to ensure that the carboxylate sidechain
10 retains a favorable electrostatic interaction with the S1 polar pocket.



15 Step 6) Link the scaffold with the moieties from steps 3, 4, and 5, preferably using the minimum number of bonds consistent with a chemically reasonable structure. Minimize the entire composite molecule in the active site of ICE.



- 120 -

Step 7) Evaluate the energy of the molecule when it has the conformation necessary for binding to ICE. Then minimize and reevaluate the energy -- this is the free conformation energy. The strain energy for binding of the potential inhibitor to ICE is the difference between the free conformation energy and the bound conformation energy. The strain energy should be less than about 10 kcal/mol. In this case the bound conformation energy is -1.6 kcal/mol and the free conformation energy is -11.7 kcal/mol, for a strain energy of 10.1 kcal/mol.

Step 8) The inhibitor designed using the above steps has been made and has been shown to have a K_i of 150 nM.

Example 2

We obtained inhibition constants (K_i) and IC_{50} values for several compounds of this invention using the three methods described below:

20 1. Enzyme assay with UV-visible substrate

This assay is run using an Succinyl-Tyr-Val-Ala-Asp-pNitroanilide substrate. Synthesis of analogous substrates is described by L. A. Reiter (Int. J. Peptide Protein Res. 43, 87-96 (1994)). The assay mixture contains:

25 65 μ l buffer (10mM Tris, 1 mM DTT, 0.1% CHAPS @pH 8.1)
10 μ l ICE (50 nM final concentration to give a rate of ~1mOD/min)
5 μ l DMSO/inhibitor mixture
30 20 μ l 400 μ M Substrate (80 μ M final concentration)
100 μ l total reaction volume

The visible ICE assay is run in a 96-well microtiter plate. Buffer, ICE and DMSO (if inhibitor

- 121 -

is present) are added to the wells in the order listed. The components are left to incubate at room temperature for 15 minutes starting at the time that all components are present in all wells. The microtiter plate reader is set to incubate at 37°C. After the 15 minute incubation, substrate is added directly to the wells and the reaction is monitored by following the release of the chromophore (pNA) at 405 - 603 nm at 37°C for 20 minutes. A linear fit of the data is performed and the rate is calculated in mOD/min. DMSO is only present during experiments involving inhibitors, buffer is used to make up the volume to 100 μ l in the other experiments.

2. Enzyme Assay with Fluorescent Substrate

This assay is run essentially according to Thornberry et al. (Nature 356: 768-774 (1992)), using substrate 17 referenced in that article. The substrate is: Acetyl-Tyr-Val-Ala-Asp-amino-4-methylcoumarin (AMC). The following components are mixed:

65 μ l buffer (10mM Tris, 1mM DTT, 0.1% CHAPS @pH8.1)
10 μ l ICE (2 - 10 nM final concentration)
5 μ l DMSO/inhibitor solution
20 μ l 150 μ M Substrate (30 μ M final)
100 μ l total reaction volume

The assay is run in a 96 well microtiter plate. Buffer and ICE are added to the wells. The components are left to incubate at 37°C for 15 minutes in a temperature-controlled wellplate. After the 15 minute incubation, the reaction is started by adding substrate directly to the wells and the reaction is monitored @37°C for 30 minutes by following the release of the AMC fluorophore using an excitation wavelength for 380 nm and an emission wavelength of 460 nm. A linear fit of the data for each well is performed and a

- 122 -

rate is determined in fluorescence units per second.

For determination of enzyme inhibition constants (K_i) or the mode of inhibition (competitive, uncompetitive or noncompetitive), the rate data
5 determined in the enzyme assays at varying inhibitor concentrations are computer-fit to standard enzyme kinetic equations (see I. H. Segel, Enzyme Kinetics, Wiley-Interscience, 1975).

3. Cell assay

10 IL-1 β Assay with a Mixed Population of Human Peripheral Blood Mononuclear Cells (PBMC)
or Enriched Adherent Mononuclear Cells

Processing of pre-IL-1 β by ICE can be measured in cell culture using a variety of cell
15 sources. Human PBMC obtained from healthy donors provides a mixed population of lymphocyte subtypes and mononuclear cells that produce a spectrum of interleukins and cytokines in response to many classes of physiological stimulators. Adherent mononuclear
20 cells from PBMC provides an enriched source of normal monocytes for selective studies of cytokine production by activated cells.

Experimental Procedure:

An initial dilution series of test compound
25 in DMSO or ethanol is prepared, with a subsequent dilution into RPMI-10% FBS media (containing 2 mM L-glutamine, 10 mM HEPES, 50 U and 50 ug/ml pen/strep) respectively to yield drugs at 4x the final test concentration containing 0.4% DMSO or 0.4% ethanol.
30 The final concentration of DMSO is 0.1% for all drug dilutions. A concentration titration which brackets the apparent K_i for a test compound determined in an ICE inhibition assay is generally used for the primary compound screen.

35 We generally test 5-6 compound dilutions and

- 123 -

have performed the cellular component of the assay in duplicate, with duplicate ELISA determinations on each cell culture supernatant.

PBMC Isolation and IL-1 Assay:

5 Buffy coat cells isolated from one pint human blood (yielding 40-45 ml final volume plasma plus cells) are diluted with media to 80 ml and LeukoPREP separation tubes (Becton Dickinson) are each overlaid with 10 ml of cell suspension. After 15 min
10 centrifugation at 1500-1800 xg, the plasma/media layer is aspirated and then the mononuclear cell layer is collected with a Pasteur pipette and transferred to a 15 ml conical centrifuge tube (Corning). Media is added to bring the volume to 15 ml, gently mix the
15 cells by inversion and centrifuge at 300 xg for 15 min. Resuspend the PBMC pellet in a small volume of media, count cells and adjust to 6×10^6 cells/ml.

 For the cellular assay, add 1.0 ml of the cell suspension to each well of a 24-well flat bottom
20 tissue culture plate (Corning), 0.5 ml test compound dilution and 0.5 ml LPS solution (Sigma #L-3012; 20 ng/ml solution prepared in complete RPMI media; final LPS concentration 5 ng/ml). The 0.5 ml additions of test compound and LPS are usually sufficient to mix the
25 contents of the wells. Three control mixtures are run per experiment, with either LPS alone, solvent vehicle control, and/or additional media to adjust the final culture volume to 2.0 ml. The cell cultures are incubated for 16-18 hr at 37°C in the presence of 5%
30 CO₂.

 At the end of the incubation period, cells are harvested and transferred to 15 ml conical centrifuge tubes. After centrifugation for 10 min at 200 xg, supernatants are harvested and transferred to
35 1.5 ml Eppendorf tubes. It may be noted that the cell

- 124 -

pellet may be utilized for a biochemical evaluation of pre-IL-1 β and/or mature IL-1 β content in cytosol extracts by western blotting or ELISA with pre-IL-1 β specific antisera.

5 Isolation of Adherent Mononuclear cells:

PBMC are isolated and prepared as described above. Media (1.0 ml) is first added to wells followed by 0.5 ml of the PBMC suspension. After a one hour incubation, plates are gently shaken and nonadherent
10 cells aspirated from each well. Wells are then gently washed three times with 1.0 ml of media and final resuspended in 1.0 ml media. The enrichment for adherent cells generally yields $2.5-3.0 \times 10^5$ cells per well. The addition of test compounds, LPS, cell
15 incubation conditions and processing of supernatants proceeds as described above.

ELISA:

We have used Quantikine kits (R&D Systems) for measurement of mature IL-1 β . Assays are performed
20 according to the manufacturer's directions. Mature IL-1 β levels of about 1-3 ng/ml in both PBMC and adherent mononuclear cell positive controls are observed. ELISA assays are performed on 1:5, 1:10 and 1:20 dilutions of supernatants from LPS-positive
25 controls to select the optimal dilution for supernatants in the test panel.

The inhibitory potency of the compounds can be represented by an IC_{50} value, which is the concentration of inhibitor at which 50% of mature IL-1 β
30 is detected in the supernatant as compared to the positive controls.

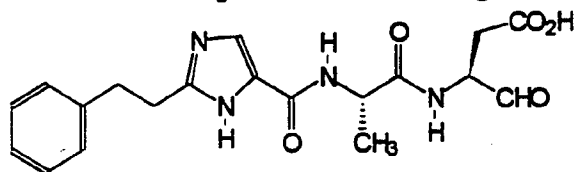
The following K_i and IC_{50} values were determined for compounds A through N using the indicated assays. Structures for compounds A through N
35 follow this table.

- 125 -

Compound K_i (μ M), by indicated assay:			
	<u>UV-visible</u> K_i (μ M)	<u>Fluorescence</u> K_i (μ M)	<u>Cell</u> IC_{50} (μ M)
5	A	5.5	25.0
	B	8.6	20.0
	C	10	>30
	D	4.7	
	E	3.2	
10	F	0.15	2 - 4
	G	4.8	
	H	0.023	0.0047
	I	0.0072	0.0052
	J	0.012	0.0039
15	K	0.010	0.002
	L	0.014	
	M	0.15	
	N	0.95	

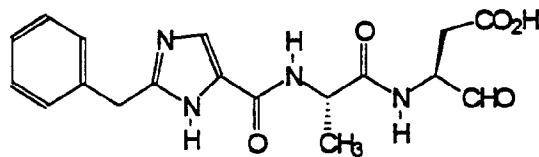
Structures of compounds A through N:

A

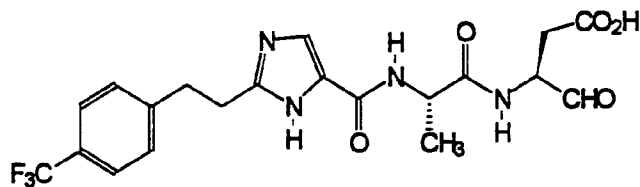


20

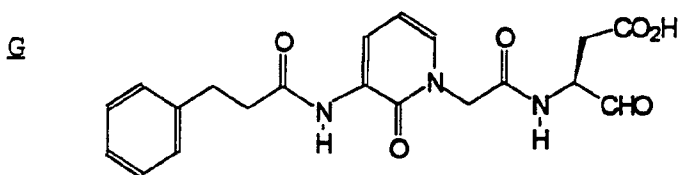
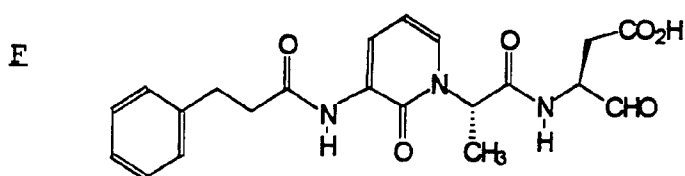
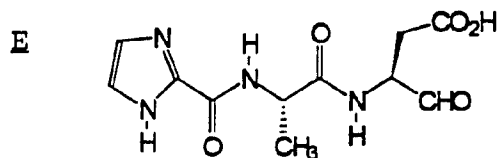
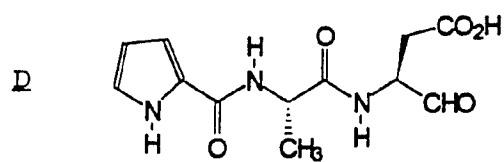
B



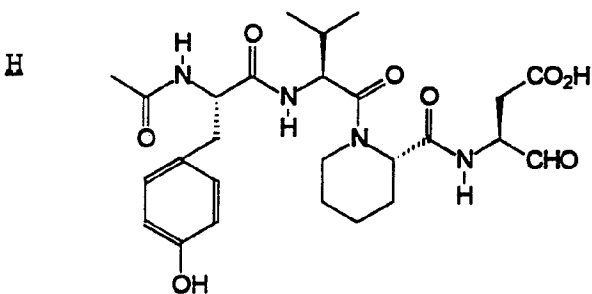
C



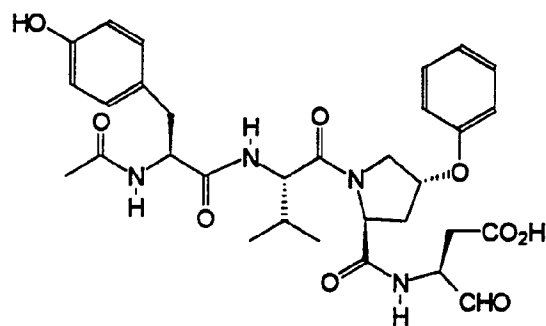
- 126 -

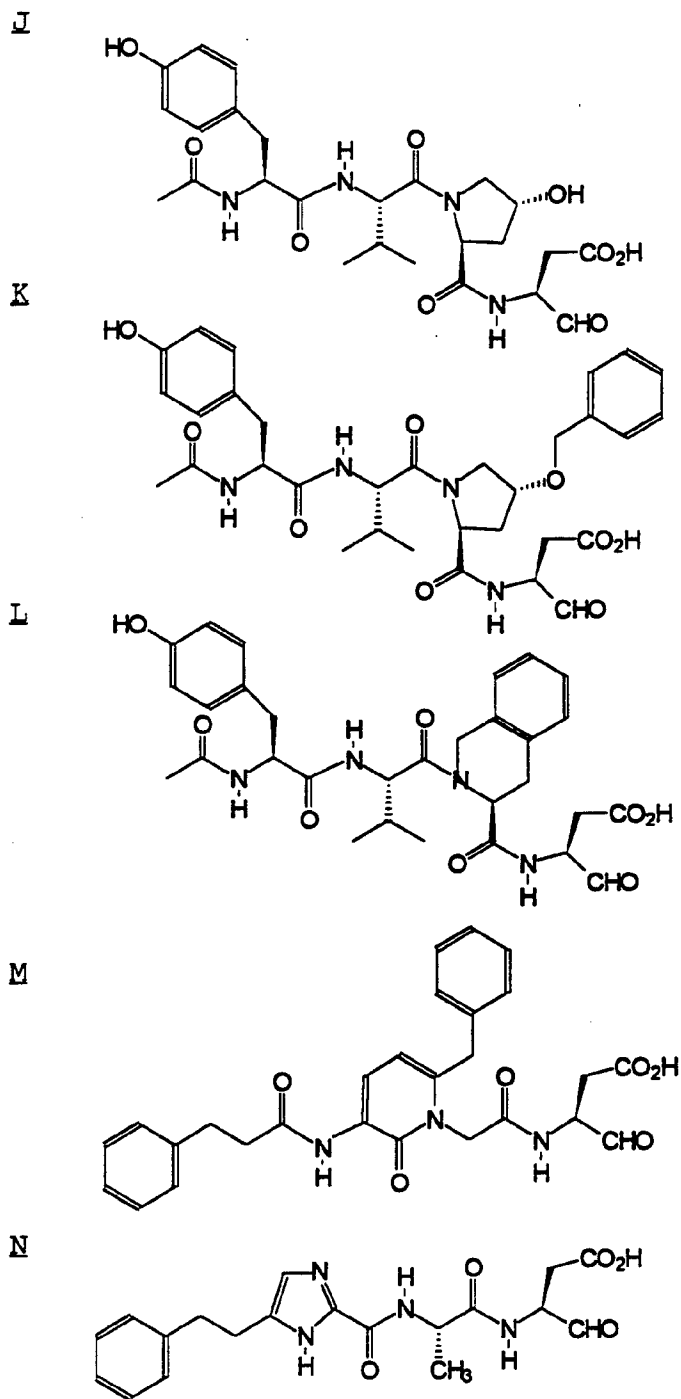


5



I





- 128 -

Example 3

Compounds of Example 2 were synthesized as follows:

5 H. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-3-amino-4-oxobutanoic acid.

Step A. N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

Reaction of N-tert-butoxycarbonylpipecolic acid (460 mg, 2.0 mmol) and N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (530 mg, 1.82 mmol) was carried out by a method analogous to that reported by Chapman (Bioorg. & Med. Chem. Lett. 1992, 2, 613-618.) to give 654 mg of the title compound.

¹H NMR (500 MHz, CDCl₃ (existing as rotamers)) δ
15 7.35 (m, 5H), 6.88 (br. s, 1H), 4.9-4.45 (m, 4H), 3.95 (br. m, 2H), 3.06 (m, 1H), 2.9 (m, 1H), 2.7 (br. m, 1H), 2.45 (m, 1H), 2.2 (m, 1H), 1.7-1.5 (m, 3H), 1.45 (two s, 9H).

20 Step B. N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

N-(N-tert-Butoxycarbonylpipecolyl)-4-amino-5-benzyloxy-2-oxo-tetrahydrofuran (654 mg) was dissolved in 15 ml of 25% trifluoroacetic acid in dichloromethane and stirred at room temperature. The mixture was concentrated to give a gummy residue. The residue was dissolved in dichloromethane and washed with 10% sodium bicarbonate. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated to give 422 mg of the title compound as a beige solid.

- 129 -

¹H NMR (500 MHz, CDCl₃) δ 7.38 (m, 5H), 7.15 (d, 1H), 5.55 (d, 1H), 4.95-4.8 (m, 1H), 4.78 (m, 1H), 4.65 (d, 1H), 4.45 (m, 1H), 3.2 (m, 0.5H), 3.05 (m, 0.5H), 2.95 (m, 0.5H), 2.85 (m, 0.5H), 2.65 (m, 1H), 2.55-2.38 (m, 1H), 1.95 (m, 1H), 1.8 (m, 1H), 1.6 (m, 2H), 1.38 (m, 2H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran.

N-Acetyl-tyrosinyl-valine (464 mg, 1.44 mmol) and N-Pipecolyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (412 mg, 1.3 mmol) were dissolved in 5 ml each of dimethylformamide and dichloromethane and cooled to 0°C. To the cooled solution was added 1-hydroxybenzotriazole (HOBT; 210 mg, 1.56 mmol) followed by the addition of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC; 326 mg, 1.7 mmol). After stirring for 18 hours, the mixture was diluted with ethyl acetate and washed with water, 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and water. The organic layer was concentrated to give a crude solid that was purified by flash chromatography (SiO₂) eluting with 94:6:1 (dichloromethane:isopropanol:pyridine) to give 370 mg of the title compound.

¹H NMR (500 MHz, CD₃OD (existing as diastereomers as well as rotamers)) δ 7.35 (m, 5H), 7.05 (m, 2H), 6.68 (m, 2H), 5.65 & 5.25 (m, 1H), 4.9-3.95 (m, 8H), 3.4-2.6 (m, 4H), 2.5-2.1 (m, 1H), 1.98 (s, 1H), 1.9 (s, 1H), 1.85 (s, 1H), 1.8-1.6 (m, 2H), 1.55-1.3 (m, 4H), 0.95-0.85 (m, 6H).

- 130 -

Step D. N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-
3-amino-4-oxobutanoic acid.

To a solution of 100 mg of N-(N-Acetyl-tyrosinyl-valinyl-pipecolyl)-4-amino-5-benzyloxy-2-oxotetrahydrofuran in 10 ml of methanol was added 60 mg of Pd(OH)₂ on carbon and the mixture placed under an atmosphere of hydrogen via a balloon. The mixture was filtered through Celite and concentrated providing a white solid. This crude solid was dissolved in 2 ml of methanol and triturated with diethyl ether affording 26 mg of the title compound.

¹H NMR (500 MHz, CD₃OD (existing as diastereomers as well as rotamers)) δ 7.1 (m, 2H), 6.7 (m, 2H), 5.2 (br. m, 1H), 4.8-3.6 (m, 6H), 3.2-2.5 (m, 4H), 2.5-2.1 (m, 1H), 1.95 (three s, 3H), 1.9-1.3 (m, 6H), 1.1-0.7 (m, 6H).

The following compounds were prepared by a method analogous to that reported for H:

J. N-[N-Acetyl-tyrosinyl-valinyl-(4-hydroxyprolinyl)]-
3-amino-4-oxobutanoic acid

Substitute N-tert-butoxycarbonyl-4-benzyloxyproline for N-tert-butoxycarbonylpipecolic acid.

L. N-[2-(N-Acetyl-tyrosinyl-valinyl)-(S)-1,2,3,4-
tetrahydroisoquinoline-3-carbonyl]-3-amino-
oxobutanoic acid

Substitute (S)-N-tert-butoxycarbonyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid for N-tert-butoxycarbonylpipecolic acid.

- 131 -

I. N-(N-Acetyl-tyrosinyl-valinyl-(4-phenoxyprolinyl))-3-amino-4-oxobutanoic acid.

Step A. N-tert-Butoxycarbonyl-4-phenoxyproline methyl ester.

5 To a cooled solution (0° C) of N-tert-butoxy-cis-4-hydroxyproline (2.0 g, 8.15 mmol), phenol (0.77 g, 8.15 mmol), and triphenylphosphine (2.14 g, 8.15 mmol) in 20 ml of tetrahydrofuran was added diethyl azodicarboxylate (1.4 ml, 9 mmol) dropwise over 30
10 minutes. The reaction was stirred at room temperature for 16 hrs. then concentrated to give a viscous residue. The crude residue was purified by flash chromatography (SiO₂) eluting with 3:7 (ethyl acetate:hexane) to give 1.89 g of the title compound.

15 ¹H NMR (500 MHz, CDCl₃) δ 7.3 (m, 2H), 6.95 (m, 1H), 6.85 (d, 2H), 4.9 (m br., 1H), 4.55-4.15 (m, 2H), 3.88-3.65 (m, 1H), 3.70 (s, 3H), 2.58 (m, 1H), 2.22 (m, 1H), 1.4 (3 x s, 9H).

20 Step B. 4-Phenoxyproline methyl ester hydrochloride.

 To a cooled solution (ice bath) of N-tert-Butoxycarbonyl-4-phenoxyproline methyl ester (0.6 g) in 20 ml of ethyl acetate was bubbled anhydrous hydrogen chloride until saturated. The mixture was warmed to
25 room temperature and stirred for 3 hrs. then concentrated to give 480 mg of the title compound.

¹H NMR (500 MHz, CDCl₃) δ 7.22 (m, 2H), 6.95 (m, 1H), 6.83 (m, 2H), 5.1 (br., 1H), 4.6 (br. m, 1H), 4.06

- 132 -

(br. m, 1H), 3.75 (s, 3H), 3.55 (br. m, 1H), 2.58 (m, 2H).

Step C. N-Acetyl-tyrosinyl-valinyl-(4-phenoxy)proline methyl ester.

5 N-Acetyl-tyrosinyl-valine (0.524 g, 1.63 mmol) and 4-phenoxyproline methyl ester (0.381 g, 1.48 mmol) were dissolved in 4 ml each of dimethylformamide and dichloromethane and cooled to 0° C. To the cooled solution was added diisopropylethylamine (258 ul, 1.86 mmol), HOBT (0.24 g, 1.78 mmol), and EDC (0.37 g, 1.92 mmol) and the reaction was stirred for 18 hrs. The mixture was diluted with 400 ml of ethyl acetate and washed with water, 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and water. The organic layer was concentrated to give a residue that was purified by flash chromatography (SiO₂) eluting with 94:6:1 (CH₂Cl₂:i-PrOH:Pyridine) to afford 360 mg of the title compound.

¹H NMR (500 MHz, CDCl₃ (existing as rotamers)) δ
20 7.3 (m, 2H), 7.05 (m, 1H), 6.95 (d, 2H), 6.9-6.2 (4 x d, 4H), 5.05 (br. s, 1H), 4.7-3.94 (m, 5H), 2.93 (m, 1H), 2.82 (m, 1H), 2.65 (m, 1H), 2.2 (m, 1H), 2.05 (m, 1H), 1.95 (s, 3H), 1.86, (m, 1H), 0.98 (d, 3H), 0.88 (d, 3H).

25 Step D. N-Acetyl-tyrosinyl-valinyl-(4-phenoxy)proline.

Lithium hydroxide (57 mg, 1.37 mmol) was added to a solution of N-Acetyl-tyrosinyl-valinyl-(4-phenoxy)proline methyl ester (360 mg, 0.685 mmol)
30 dissolved in 8 ml of tetrahydrofuran/water (1:1) and

- 133 -

stirred at room temperature for 1 hour. The mixture was acidified with 10% hydrochloric acid giving a white precipitate that was collected to give 175 mg of the title compound.

5 ¹H NMR (500 MHz, DMSO-d₆) δ 9.2 (br. s, 1H),
8.05-7.95 (m, 2H), 7.3 (m, 1H), 7.0-6.9 (m, 4H), 6.65
(d, 2H), 4.42 (m, 1H), 4.35 (m, 1H), 4.05-3.95 (m, 2H),
3.3 (br. s, 2H), 2.75 (m, 1H), 2.55-2.38 (m, 2H), 2.2
(m, 1H), 2.0 (m, 1H), 1.7 (s, 3H), 0.95 (d, 3H), 0.85
10 (d, 3H).

Step E. N-[N-Acetyl-tyrosinyl-valinyl-(4-
phenoxy)prolinyl]-4-amino-5-benzyloxy-2-
oxotetrahydrofuran.

15 The title compound was prepared by the method
reported for compound H, step A, by reaction of N-
acetyl-tyrosinyl-valinyl-(4-phenoxy)proline and N-
allyloxycarbonyl-4-amino-5-benzyloxytetrahydrofuran.

20 ¹H NMR (500 MHz, CDCl₃, (existing as a 1:1
diastereomer mixture of the hemiacetal)) δ 7.8-6.3 (m,
17H), 5.6 (d, 1H), 5.1-4.15 (m, 5H), 4.15-3.75 (m, 2H),
2.95-2.15 (m, 5H), 2.15-1.95 (m, 1H), 1.9-1.85 (2 x s,
3H), 1.1-0.75 (m, 6H).

25 Step F. N-[N-Acetyl-tyrosinyl-valinyl-(4-
phenoxy)prolinyl]-3-amino-4-oxobutanoic
acid.

The title compound was prepared by the
hydrogenolysis procedure reported for compound H,
step D.

- 134 -

¹H NMR (500 MHz, CD₃OD (existing as a 1:1 diastereomer mixture of the hemiacetal)) δ 7.25 (m, 2H), 7.10-6.85 (m, 5H), 6.65 (d, 2H), 5.1 (br. m, 1H), 4.65-4.05 (m, 5H), 4.0-3.40 (m, 2H), 2.95-2.35 (m, 5H), 2.25 (m, 1H), 2.05 (m, 1H), 1.85 (s, 3H), 1.0 (d, 3H), 0.95 (d, 3H).

K. N-[N-Acetyl-tyrosinyl-valinyl-(4-benzyloxy)prolinyl]-3-amino-4-oxobutanoic acid.

Step A. N-(N-Allyloxycarbonyl-4-benzyloxyprolinyl)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by the reaction of N-allyloxycarbonyl-4-benzyloxyproline and 3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (T.L. Graybill et. al., Abstracts of papers, 206th National Meeting of the American Chemical Society, Abstract MEDI-235. Chicago, IL. (1993)) under similar peptide coupling conditions as reported above (compound H; Step C).

¹H NMR (500 MHz, CDCl₃) δ 9.05 (br. s, 1H), 7.85 (br. m, 1H), 7.4-7.2 (m, 5H), 7.15 (br. s, 1H), 6.55 (br. s, 1H), 5.9 (m, 1H), 5.1-4.9 (br. m, 2H), 4.65-4.4 (m, 4H), 4.2 (br. m, 1H), 3.75-3.5 (m, 2H), 2.75-2.55 (m, 2H), 2.5 (br. m, 1H), 2.25 (br. m, 1H) 1.4 (s, 9H).

Step B. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid tert-butyl ester semicarbazone.

The title compound was prepared by reaction of N-acetyl-tyrosinyl-valine and N-(N-allyloxycarbonyl-4-

- 135 -

benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone by reaction conditions reported for compound H, step A.

¹H NMR (500MHz, CD₃OD) δ 7.35-7.2 (m, 6H), 7.0 (d, 2H), 6.65(d, 2H), 4.85 (m, 1H), 4.6-4.45 (m, 4H), 4.3 (br. m, 1H), 4.15 (m, 1H), 3.7 (m, 1H), 2.95 (m, 1H), 2.75-2.6 (m, 3H), 2.35 (m, 1H), 2.1 (m, 1H), 1.9 (s, 3H), 1.4 (s, 9H), 0.95 (d, 3H), 0.90 (s, 3H).

Step C. N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4oxobutanoic acid.

N-(N-Acetyl-tyrosinyl-valinyl-(4-benzyloxyprolinyl))-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (270 mg) was dissolved into 10 ml of 25% trifluoroacetic acid in dichloromethane and stirred at room temperature for 3 hours. The mixture was concentrated to give a solid residue. The residue was dissolved into a 10 ml mixture of methanol:acetic acid:37% formaldehyde (3:1:1) and stirred at room temperature for 1 hour. The mixture was concentrated and the resulting residue purified by flash chromatography (SiO₂) eluting with dichloromethane/methanol/formic acid (100:5:0.5) to give 37 mg of the title compound.

¹H NMR (500 MHz, CD₃OD (existing as a 1:1 mixture of diastereomers of the hemiacetal)) δ 7.4-7.25 (m, 5H), 7.0 (d, 2H), 6.65 (d, 2H), 4.65-4.05 (m, 7H), 3.75-3.4 (m, 2H), 3.05-2.3 (m, 5H), 2.2-1.95 (m, 2H), 1.90 (s, 3H), 1.0 (d, 3H), 0.95 (d, 3H).

- 136 -

Example 4

We obtained inhibition constants (K_i) and IC_{50} values for several compounds of this invention using enzyme assays with UV-visible substrate and cell assays as described in Example 2. The following K_i and IC_{50} values were determined for compounds 7a, 7b, 20a-d, 21c-f, 22e, 25, 28, 33a-c, 36a, 36b, 39, 43, 47a, 47b, 54a-l, 63, 69a, 69b, 84a and 84b using the indicated assays. Corresponding lettered compound designations are indicated parenthetically. The compound structures are shown in Examples 2 and 5.

	<u>Compound</u>	<u>Assay</u>	
		<u>UV-visible</u> K_i (μ M)	<u>Cell</u> IC_{50} (μ M)
15	7a	35	
	7b	1.2	
	20a (= E)	3.2	
	20b	0.85	16.4
	20c (= N)	0.95	
20	20d	0.1	6.2
	21c	0.64	
	21d	0.24	4.8
	21e	0.22	2.9
	21f	0.17	2.9
25	22e	0.19	
	25	6.2	
	28	12.0	
	33a (= A)	5.5	25.0
	33b (= C)	10.0	>30.0
30	33c (= B)	8.6	20.0
	36a (= D)	4.7	
	36b	0.8	17.0
	39	2.5	
	43	20.0	

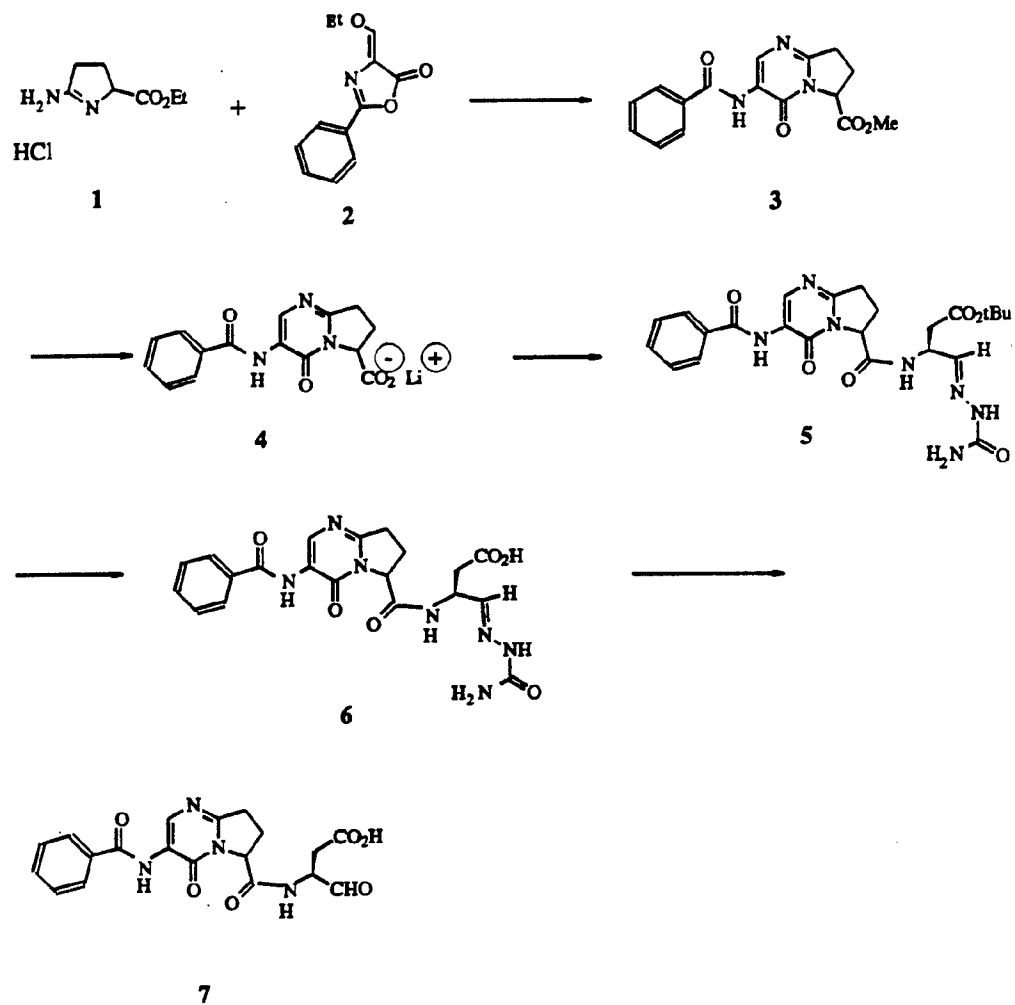
- 137 -

	47a		0.019	2.1
	47b		0.027	1.8
	54a	(= <u>F</u>)	0.15	2.7
	54b	(= <u>M</u>)	0.15	9.1
5	54c		1.2	>19.0
	54d		1.0	
	54e		3.5	
	54f		0.9	
	54g	(= <u>G</u>)	4.8	>20.0
10	54h		0.97	
	54i		0.054	2.4
	54j		0.28	
	54k		0.085	
	54l		0.215	7.0
15	63	(= <u>Q</u>)	0.85	4.1
	69a	(= <u>R</u>)	0.011	0.735
	69b	(= <u>S</u>)	0.050	0.745
	84a	(= <u>V</u>)	0.100	3.3
	84b	(= <u>W</u>)	0.019	0.50

- 138 -

Example 5

Compounds of Example 4 were synthesized as follows:



- 139 -

3-Benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carboxylic acid methyl ester (3). A mixture of (4S)-2-amino-1-pyrroline-5-carboxylic acid ethyl ester hydrochloride (1, 0.44g, 2.38mmol; prepared in an analogous fashion as the methyl ester as described by Lee and Lown, J. Org. Chem., 52, 5717-21 (1987)); 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one (2, 0.50g, 2.31mmol) and sodium methoxide (0.12g, 2.22mmol) in ethanol (10ml) was refluxed for 2h. The reaction was allowed to cool to room temperature and concentrated in vacuo. The residue was suspended in water and 1N sulfuric acid was added until pH 1 was reached. The aqueous mixture was extracted with dichloromethane, the organic layer was separated and concentrated in vacuo to yield 0.6g of a orange solid. Chromatography (flash, SiO₂, 60% ethyl acetate/hexane increased to 100% ethyl acetate stepwise gradient, then 10% methanol/dichloromethane) to give 0.5g of an orange solid. A mixture of the orange solid and potassium cyanide (0.03g, 0.5mmol) in methanol (10ml) was refluxed overnight. The cooled reaction was concentrated in vacuo to give a yellow solid. Chromatography (flash, SiO₂, 40% ethyl acetate/hexane to 100% ethyl acetate stepwise gradient) afforded 0.22g (31.6%) of the title compound: ¹H NMR (d₆-DMSO) δ 2.25 (m, 1H), 2.65 (m, 1H), 3.15 (m, 2H), 3.75 (s, 3H), 5.15 (dd, 1H), 7.5 (t, 2H), 7.6 (t, 1H), 7.95 (d, 2H), 8.6 (s, 1H), 9.5 (s, 1H).

(3S) - [(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid tert-butyl ester semicarbazone (5a and 5b). A mixture of 3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carboxylic acid ethyl ester (3, 0.22g 0.70mmol) and lithium hydroxide

- 140 -

hydrate (0.032g, 0.76mmol) in methanol (5ml) and tetrahydrofuran (5ml) and was stirred 18h at room temperature. The reaction was concentrated to give 3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-
5 a]pyrimidine-6-carboxylic acid lithium salt (4) as a white solid. This was used without further purification in the subsequent reaction.

A 0°C mixture of (3S)-amino-4-oxo-butanoic acid tert-butyl ester semicarbazone (0.163g, 0.71mmol; Graybill et al., Int. J. Protein Res., 44, pp. 173-82 (1994)) and 3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carboxylic acid lithium salt (4) in dimethylformamide (5ml) and dichloromethane (5ml) was treated with hydroxybenzotriazole (0.104g, 15 0.77mmol) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrogen chloride (0.148g, 0.37mmol). The reaction was allowed to warm to room temperature and stirred 18hr. The reaction was poured onto water (50ml) and extracted with ethyl acetate (2 x 50mL).
20 The combined organic layers were washed with aqueous 1M sodium hydrogen sulfate solution, dilute aqueous sodium hydrogen carbonate (50mL) and saturated aqueous sodium chloride. The organic layer was concentrated in vacuo to yield 0.43g of a yellow solid. Chromatography
25 (flash, SiO₂, ammonium hydroxide/methanol/dichloromethane (1:1:99 to 1:10:90 stepwise gradient)) gave 0.11g (30.9%) of the higher R_f diastereomer (5a): ¹H NMR (CD₃OD) δ 1.45 (s, 9H), 2.29-2.35 (m, 1H), 2.6-2.7 (m, 2H), 2.8 (dd, 1H), 3.1-3.15 (m, 1H), 3.2-3.3 (m, 1H), 4.9-4.95 (m, 1H), 5.2 (dd, 1H), 7.25 (d, 1H), 7.5-7.55 (m, 2H), 7.55-7.6 (m, 1H), 7.95 (d, 2H), 8.9 (s, 1H) and 0.11g (30.9%) of the lower R_f diastereomer (5b): ¹H NMR (CD₃OD) δ 1.45 (s, 9H), 2.3-2.4 (m, 1H), 2.6-2.7 (m, 1H), 2.7-2.8 (m, 2H), 3.1-3.15 (m, 1H),
35 3.2-3.3 (m, 1H), 4.85-4.95 (m, 1H), 5.15 (dd, 1H), 7.25

- 141 -

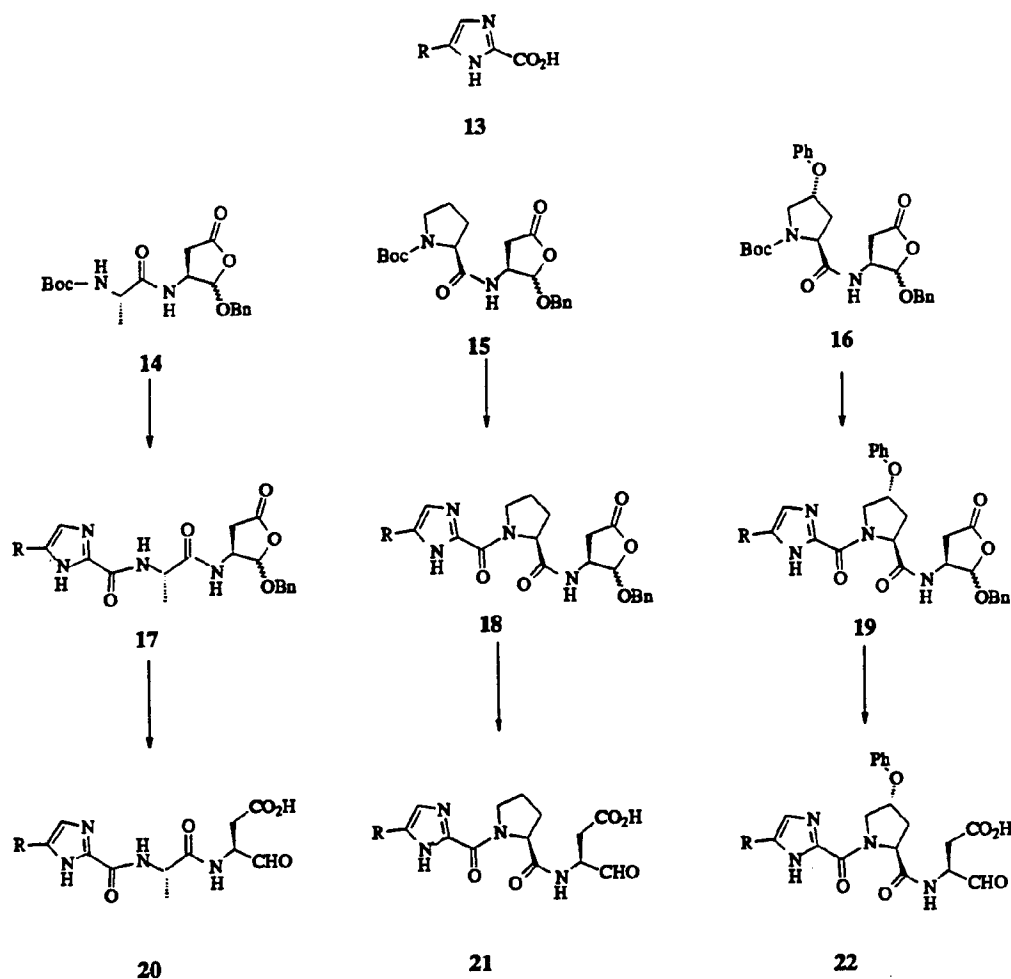
(d, 1H), 7.55 (t, 2H), 7.6 (t, 1H), 7.95 (d, 2H), 8.9 (s, 1H). Diastereomer 5a and diastereomer 5b were taken on separately.

(3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid (7a). A suspension of (3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid tert-butyl ester semicarbazone (5a, 0.11g, 0.22mmol) in dichloromethane (7.5ml) and trifluoroacetic acid (2.5ml) was stirred for 5h. The reaction was concentrated in vacuo, the residue was taken up in dichloromethane, concentrated in vacuo, suspended in toluene and concentrated in vacuo to give 0.07 g of (3S)-[(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid semicarbazone (6a) as a white solid. The solid was suspended in a mixture of 37% aqueous formaldehyde/acetic acid/methanol (1:1:5) and stirred at room temperature for 18hr. The reaction was concentrated in vacuo, the residue was suspended in acetonitrile and concentrated in vacuo to give 0.1g of a white solid. Chromatography (HPLC, reverse phase C18, 1% to 75% acetonitrile/water (buffered with 0.1% trifluoroacetic acid) gradient elution) to give 0.05g (60%) of 7a as a white solid: RT = 7.9 min (HPLC, C18 reverse phase, 1 to 100% acetonitrile/water (0.1% trifluoroacetic acid buffer); 20 min gradient elution); ¹H NMR (CD₃OD (existing as a 1:1 mixture of anomers of the hemi-acyloxy acetal form)) δ 2.25-2.4 (m, 1H), 2.45-2.8 (m, 4H), 3.05-3.15 (m, 1H), 4.25-4.35 (m, 1H), 4.55-4.6 (m, 1H), 5.1-5.2 (m, 1H), 7.45-7.65 (m, 3H), 7.9-8.0 (m, 2H), 8.9 (s, 1H).

- 142 -

(3S) - [(3-benzoylamino-4-oxo-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-6-carbonyl)-amino]-4-oxo-butanoic acid (7b) was prepared as described for diastereomer 7a to give 0.03g (35%) of 7b as a white solid: RT = 8.1 min (HPLC, C18 reverse phase, 1 to 100% acetonitrile/water (0.1% trifluoroacetic acid buffer); 20 min gradient elution); ¹H NMR (d₆-DMSO (existing as a 1:1 mixture of anomers of the hemi-acyloxy acetal form)) δ 2.1-2.2 (m, 1H), 2.4 (d, 1H), 2.7-2.8 (m, 1H), 3.0-3.2 (m, 3H), 5.0 (dd, 1H), 5.1-5.2 (m, 1H), 5.5 (s, 1H), 5.7-5.8 (m, 1H), 7.55 (t, 2H), 7.67 (t, 1H), 7.95 (d, 2H), 8.55 (s, 1H), 9.0-9.15 (m, 1H), 9.4-9.5 (m, 1H).

- 143 -



- a** $R = H$
b $R = PhCH_2$
c $R = Ph(CH_2)_2$
d $R = Ph(CH_2)_3$
e $R = 4MeO-Ph(CH_2)_3$
f $R = 4HO-Ph(CH_2)_3$

5

Imidazole-2-carboxylic acids 13 were prepared using modifications of described procedures (Yamanaka et al., Chem. Pharm. Bull., 31, pp. 4549-53 (1983)); Suzuki et al., J. Org. Chem., 38, pp. 3571-75 (1973)); and Oliver et al. (J. Org. Chem., 38, pp. 1437-38 (1973)).

10

- 144 -

Imidazole-2-carboxylic acid (13a) was prepared according to Curtis and Brown, J. Org. Chem., 45, pp. 4038-40 (1980).

5 4-Benzylimidazole-2-carboxylic acid (13b), was isolated as an off-white solid: mp. 153-155°C; IR (KBr) 3026-2624, 1630, 1515, 1498, 1438, 1405; ¹H NMR(d₆-DMSO) δ 7.31 (5H, m), 7.14 (1H, s), 3.95 (2H, s).

10 4-(2-Phenylethyl)imidazole-2-carboxylic acid (13c), was isolated as a pale yellow solid: mp. 151-153°C; IR (KBr) 3054-2617, 1637, 1497, 1376; ¹H NMR(d₆-DMSO) δ 7.27 (5H, m), 7.11 (1H, s), 2.92 (4H, s).

15 4-(3-Phenylpropyl)imidazole-2-carboxylic acid (13d), was isolated as a pale yellow solid: mp. 148-150°C; IR (KBr) 3020-2615, 1636, 1509, 1498, 1383; ¹H NMR(d₆-DMSO) δ 7.35-7.22 (5H, m), 7.01 (1H, s), 2.62 (4H, m), 1.94 (2H, m).

20 4-[3-(4-Methoxyphenyl)propyl]imidazole-2-carboxylic acid (13e), was isolated as a white crystalline solid: mp. 155-156°C (decomp.); IR (KBr) 3300-2300, 1633, 1513, 1376, 1244; ¹H NMR(d₆-DMSO) δ 9.50-7.50 (2H, bs), 7.15 (1H, s), 7.11 (2H, d, J=8.5), 6.84 (2H, d, J=8.5), 3.71 (3H, s), 2.60-2.50 (4H, m), 1.86 (2H, m). Anal. Calcd for C₁₄H₁₆N₂O₃: C, 64.60; H, 6.20; N, 10.76. Found: C, 64.45; H, 6.21; N, 10.70.

25 4-[3-(4-Hydroxyphenyl)propyl]imidazole-2-carboxylic acid (13f). A solution of the ethyl ester of 13e (1.15g, 4.0mmol) in dry dichloromethane (50ml) was treated with boron tribromide (16ml, 1.0M solution in CH₂Cl₂, 16.0mmol) at 0°C. After 15min at 0°C, the

- 145 -

mixture was warmed to 25°C and stirred for 16h. The reaction mixture was cooled in an ice bath and quenched with a dropwise addition of water (20ml). The resulting mixture was briefly stirred at 25°C then
5 filtered. The filtrate was carefully neutralised by the addition of solid NaHCO₃ to afford 13f (700mg, 71%) as a white solid: m.p. 186-187°C (decomp.) (recrystallised from MeOH); IR (KBr) 3500-2400, 2935, 1640, 1516, 1396, 1232; ¹H NMR(d₆-DMSO) δ 9.83 (3H, bs),
10 7.16 (1H, s), 6.98 (2H, d, J=8.2), 6.66 (2H, d, J=8.2), 2.60-2.40 (4H, m), 1.84 (2H, m). Anal. Calcd for C₁₃H₁₄N₂O₃: C, 63.40; H, 5.73; N, 11.38. Found: C, 62.96; H, 5.70; N, 11.27.

(2R,S, 3S) N²-Tert-butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (14). Tri-n-butyl tin hydride (4.0ml, 14.9mmol) was added dropwise to a solution of (2R,S, 3S) 3-(N-allyloxycarbonyl) amino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Biorg. Med. Chem. Lett., 2, pp. 613-18 (1992); (2.91g,
20 10mmol)), N-tert-butoxycarbonyl-L-alanine (2.08g, 11mmol) and bis(triphenylphosphine)palladium (II) chloride (150mg) in dichloromethane (75ml) until the colour of the solution turned dark orange. Hydroxybenzotriazole (2.70g, 20mmol) was added, and the
25 mixture cooled to 0°C. 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (2.30g, 12mmol) was added then the mixture was allowed to warm slowly to room temperature during 4h. The mixture was diluted with ethyl acetate (250ml) and washed with 1N
30 hydrochloric acid (3 x 150ml), saturated aqueous sodium bicarbonate (3 x 150ml) and brine (2 x 150ml), then dried (MgSO₄), filtered and concentrated. The crude product was purified by column chromatography (50-70% ethyl acetate/hexane) to afford 3.17g (84%) of a

- 146 -

mixture of diastereomers. Recrystallization (ethyl acetate-hexane) gave colorless crystals: mp. 132-145°C; IR (KBr) 3357, 3345, 1781, 1688, 1661, 1535, 1517, 1165; ¹H NMR(d₆-DMSO) δ 8.49 (d, J = 6.8), 8.23 (d, J = 7.4), 7.40 (5H, m), 7.01 (1H, m), 5.68 (d, J = 5.0), 4.75 (m), 4.31 (m), 3.97 (1H, m), 2.82 (m), 3.11 (m), 2.82 (m), 2.59 (m), 2.45 (m), 1.40 (9H, s), 1.20 (d, J = 7.2), 1.16 (d, J = 7.2). Anal. Calcd for C₁₉H₂₆N₂O₆: C, 60.31; H, 6.92; N, 7.40. Found C, 60.30; H, 6.91; N, 7.38.

(2*R,S*, 3*S*) tert-Butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-prolinamide (15), was prepared by the method described for 14 to afford 1.64g (81%) of a colorless glass. IR (KBr) 3317, 2978, 1797, 1697, 1670, 1546, 1400, 1366, 1164, 1121; ¹H NMR(CDCl₃) δ 7.68 (1H, brm), 7.35 (5H, m); 5.53 (d, J=5.2), 5.43 (s), 4.93-4.61 (m), 4.44 (m), 4.25 (brm), 3.39 (2H, brm), 3.10-2.81 (1H, m), 2.44 (1H, m), 2.32 (brm), 1.88 (brm), 1.67 (brm), 1.42 (9H, s).

(2*R,S*, 3*S*) N-(N-tert-Butoxycarbonyl-(4(*R*)-phenoxy-L-prolinyl)-3-amino-2-benzyloxy-5-oxotetrahydrofuran (16) was prepared by the method described for 14 to afford 530mg (84%) of a colorless amorphous solid: ¹H NMR (CDCl₃) δ 7.65 (1H, m), 7.4-7.2 (7 H, m), 6.95 (1H, m), 6.85 (1H, m), 5.55(1H, d), 4.95 (1H, d), 4.8-4.7 (1H, brm), 4.65 (1H, d), 4.55-4.45 (1H, brm), 4.4-4.3 (0.5H, brm), 3.95-3.85 (0.5H, brm), 3.75-3.58 (2H, m), 2.95-2.8 (1H, m), 2.7-2.55 (1H, m), 2.54-2.4 (1H, m), 2.35-2.2 (1H, m), 1.4 (9H,s).

(2*R,S*, 3*S*) N²-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (17d). Trifluoroacetic acid (7ml) was

- 147 -

added to a solution of (2*R,S*, 3*S*) N²-tert-butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (14) (1.00g, 2.64mmol) in dichloromethane (7ml) at 0°C. The mixture was stirred at 0°C for 75 min. The mixture was concentrated, and the residue treated with diethyl ether then the ether was removed under vacuum. This procedure was repeated twice to yield a pale yellow glass. The solid was dissolved in DMF (20ml). Diisopropylethylamine (1.38ml, 7.92mmol) followed by 4-(3-phenylpropyl)imidazole-2-carboxylic acid (13d) (0.67g, 290mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (0.56g, 2.90mmol) and hydroxybenzotriazole (0.71g, 5.28mmol) were then added to this solution. The mixture was stirred at room temperature for 20h then poured into brine. The mixture was extracted with ethyl acetate (3 x 50ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2 x 100ml) then brine (2 x 100ml), dried (MgSO₄), filtered and concentrated. The residue was purified by column chromatography (ethyl acetate) to afford 0.99g (76%) of 17d as a mixture of diastereomers: IR (KBr) 3293, 3064, 2937, 1793, 1650, 1530, 1451, 1446, 1119; ¹H NMR (CDCl₃) δ 7.96 (brm), 7.62 (brd), 7.36-7.10 (10H, m), 6.88 (s), 6.86 (s), 5.53 (d, J=5.2), 5.48 (s), 4.87-4.52 (4H, m), 3.11-2.38 (2H, m), 2.65 (4H, m), 1.99 (2H, m), 1.47 (d, J=6.9), 1.46 (d, J=7.0).

The following compounds were prepared in a similar manner:

(2*R,S*, 3*S*) N²-(Imidazole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (17a), was

- 148 -

isolated (74%) as a pale yellow solid: IR (KBr) 3289, 3056, 2937, 1793, 1664, 1642, 1528, 1453, 1440, 1124; ¹H NMR (d₆-DMSO) δ 13.13 (1H, brs), 8.67 (d, J=7.0), 8.48 (d, J=7.8), 8.29 (d, J=6.8), 8.25 (d, J=7.6), 7.40-7.34 (6H, m), 7.11 (1H, s), 5.69 (d, J=5.0), 5.49 (d, J=0.8), 4.85-4.31 (4H, m), 3.19-2.42 (2H, m), 1.38 (d, J=7.4), 1.34 (d, J=7.4).

(2*R,S*, 3*S*) N²-(4-Benzylimidazole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (17b), was isolated (75%) as a pale yellow glass: IR (KBr) 3294, 3031, 2937, 1792, 1650, 1530, 1453, 1444, 1119; ¹H NMR(CDCl₃) δ 7.99 (brm), 7.75 (brd), 7.36-7.11 (10H, m), 6.81 (1H, s), 5.51, 5.45 (d, s, J=5.3), 4.85-4.47 (4H, m), 3.95 (2H, s), 3.04-2.72 (1H, m), 2.48-2.35 (1H, m), 1.44 (d, J=6.9), 1.43 (d, J=7.1).

(2*R,S*, 3*S*) N²-[4-(2-Phenylethyl)imidazole-2-carbonyl]-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (17c), was isolated (79%) as a pale yellow glass: IR (KBr) 3292, 3029, 2936, 1793, 1650, 1530, 1453, 1444, 1119; ¹H NMR(CDCl₃) δ 8.06 (brm), 7.70 (brs), 7.39-7.15 (10H, m), 6.82 (s), 6.81 (s), 5.53 (d, J=5.2), 5.48 (s), 4.87-4.53 (4H, m), 2.95 (4H, m), 3.11-2.37 (2H, m), 1.48 (d, J=5.6), 1.45 (d, J=6.7).

(2*R,S*, 3*S*) 1-[4-(2-Phenylethyl)imidazole-2-carbonyl]-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-prolinamide (18c), was isolated (79%) as a pale yellow glass: IR (CH₂Cl₂) 3422, 2959, 1795, 1685, 1611, 1497, 1116; ¹H NMR(d₆-DMSO) δ 12.78-12.59 (1H, m), 8.61-8.34 (1H, m), 7.39-7.22 (10H, m), 6.99-6.61 (1H, m), 5.71-5.26 (1H, m), 4.85-4.02 (4H, m), 3.63 (1H, m), 3.18-1.74 (11H, m).

- 149 -

(2*R,S*, 3*S*) 1-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-
N-(tetrahydro-2-benzyl-oxy-5-oxo-3-furanyl)-L-
prolinamide (18d), was isolated (87%) as a colorless
glass: IR (CH₂Cl₂) 3422, 3214, 2945, 1794, 1685, 1604,
1496, 1117; ¹H NMR(d₆-DMSO) δ 12.71 (1H, brm), 8.61-
8.34 (1H, m), 7.45-7.18 (10H, m), 7.05-6.64 (1H, m),
5.70-5.28 (1H, m), 4.85-4.02 (4H, m), 3.62 (1H, m)
3.18-1.71 (13H, m).

(2*R,S*, 3*S*) 1-{4-[3-(4-Methoxyphenyl)propyl]imidazole-2-
carbonyl}-N-(tetrahydro-2-benzyl-oxy-5-oxo-3-furanyl)-
L-prolinamide (18e), was isolated (72%) as a white
glassy solid: mp. 62-65°C; IR (KBr) 3213, 2937, 1793,
1680, 1606, 1606, 1512, 1245; ¹H NMR(d₆-DMSO) δ 12.71,
12.67, 12.58 (1H, 3 x bs), 8.60-8.30 (1H, m), 7.40-7.20
(5H, m), 7.15-6.55 (5H, m), 5.66-5.20 (1H, m), 4.81-
4.59 (2H, m), 4.55-4.05 (2H, m), 3.71 (3H, s), 3.65-
3.45 (1H, m), 3.15-1.50 (13H, m). FABSMS m/e 547 (M⁺,
100%), 439, 412, 340, 312, 243, 177, 154.

(2*R,S*, 3*S*) 1-{4-[3-(4-Hydroxyphenyl)propyl]imidazole-2-
carbonyl}-N-(tetrahydro-2-benzyl-oxy-5-oxo-3-furanyl)-
L-prolinamide (18f), was isolated (70%) as a light
yellow glassy solid: mp. 86-90°C; IR (KBr) 3298, 1790,
1669, 1606, 1515, 1242; ¹H NMR(d₆-DMSO) δ 12.66, 12.56
(1H, 2 x bs), 9.14 (1H, s), 8.57-8.30 (1H, m), 7.36-
7.30 (5H, m), 7.02-6.83 (3H, m), 6.70-6.57 (2H, m),
5.65-5.28 (1H, m), 4.80-4.49 (2H, m), 4.50-4.05 (2H,
m), 3.65-3.45 (1H, m), 3.15-1.55 (13H, m). FABMS m/e
533 (M⁺, 100%), 425, 298, 229, 176, 154.

1-{5-[3-(4-Methoxyphenyl)propyl]-1*H*-imidazole-2-
carbonyl}-4(*R*)-phenoxypyrrolidine-2(*S*)-carbonyl-
(tetrahydro-2(*R,S*)-benzyl-oxy-5-oxofuran-3(*S*)-yl)amide
(19e) was isolated (77%) as a clear colorless amorphous

- 150 -

solid. ^1H NMR (CDCl_3) δ 9.95-9.75 (1H, m), 7.95 (1H, brs), 7.40-7.2 (7H, m), 7.2-6.78 (7H, m), 5.65-5.6 (1H, m), 5.55-5.45 (1H, m), 5.3-5.2 (1H, m), 5.15-5.0 (1H, m), 4.95-4.75 (1H, m), 4.7-4.6 (1H, m), 4.5-4.4 (1H, m), 4.35-4.4.25 (1H, m), 3.8 (3H, s), 3.05-1.75 (10H, m).

(3S) 3-{N-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-L-alaninyl}amino-4-oxo-butanoic acid (20d). A mixture of (2R,S, 3S) N^2 -[4-(3-Phenylpropyl)imidazole-2-carbonyl]-N-(tetrahydro-2-benzylloxy-5-oxo-3-furanyl)-L-alaninamide (0.93g, 1.90mmol) and 10% palladium on activated carbon (0.93g) in methanol (100ml) was stirred under a hydrogen atmosphere for 5h. The resulting mixture was filtered and concentrated to yield a colorless glass. Recrystallization from methanol-diethyl ether afforded 401mg (53%) of 20d as a colorless solid: mp. 94-96°C; $[\alpha]_D^{27} +16.4^\circ$ (c 0.5, MeOH); IR (KBr) 3300, 3287, 1786, 1732, 1659, 1651, 1532, 1451; ^1H NMR(CD_3OD) δ 7.19 (5H, m), 6.91 (1H, s), 4.60-4.46 (2H, m), 4.27 (1H, m), 2.63 (4H, m), 2.75-2.40 (2H, m), 1.96 (2H, m), 1.44 (3H, d, $J=7.0$).

The following compounds were prepared in a similar manner:

(3S) 3-[N-(Imidazole-2-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (20a; **E**), was isolated (83%) as a colorless solid: mp. 115°C; $[\alpha]_D^{25} +4.4^\circ$ (c 0.5, MeOH); IR (KBr) 3303, 1782, 1658, 1650, 1563, 1521, 1454; ^1H NMR(CD_3OD) δ 7.18 (2H, s), 4.55 (2H, m), 4.27 (1H, m), 2.56 (2H, m), 1.45 (d, $J=7.1$), 1.44 (d, $J=7.0$).

(3S) 3-[N-(4-Benzylimidazole-2-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (20b), was isolated (56%) as a colorless solid: mp. 113-115°C; $[\alpha]_D^{29} +18.2^\circ$

- 151 -

(c 0.5 MeOH). IR (KBr) 3301, 3288, 1783, 1727, 1650, 1531, 1452; ^1H NMR(CD_3OD) δ 7.25 (5H, m), 6.90 (1H, s), 4.59-4.45 (2H, m), 4.26 (1H, m), 3.95 (2H, s), 2.74-2.39 (2H, m), 1.42 (3H, d, $J=7.0$). Anal. Calcd for $\text{C}_{18}\text{H}_{20}\text{O}_4\text{N}_5$: C, 56.69; H, 5.55; N, 14.69. Found: C, 57.06; H, 5.54; N, 14.41.

(3S) 3-{N-[4-(2-Phenylethyl)imidazole-2-carbonyl]-L-alaninyl}amino-4-oxobutanoic acid (20c; **N**), was isolated (53%) as a colorless solid: mp. 102-104°C; $[\alpha]_D^{27} +13.7^\circ$ (c 0.5, MeOH); IR (KBr) 3299, 3289, 1785, 1732, 1650, 1531, 1452; ^1H NMR(CD_3OD) δ 7.20 (5H, m), 6.82 (1H, s), 4.60-4.46 (2H, m), 4.29 (1H, m), 2.92 (4H, s), 2.76-2.41 (2H, m), 1.44 (3H, 2 x d, $J=7.1$). Anal. Calcd for $\text{C}_{19}\text{H}_{22}\text{N}_4\text{O}_5$ H_2O : C, 56.43; H, 5.98; N, 13.85. Found: C, 56.65; H, 5.84; N, 13.91.

(3S) 3{N-[4-(2-Phenylethyl)imidazole-2-carbonyl]-L-prolinyl}amino-4-oxobutanoic acid (21c), was isolated (85%) as a colorless glass: mp. 101-103°C (methanol-diethyl ether); $[\alpha]_D^{27} -63.8^\circ$ (c 0.25, MeOH); IR (KBr) 3275, 1784, 1728, 1664, 1606, 1498, 1429; ^1H NMR(CD_3OD) δ 7.24 (5H, m), 6.83 (s), 6.79 (s), 4.58-4.14 (3H, m), 3.69 (1H, m), 2.93 (4H, brs), 2.75-1.99 (6H, m). Anal. Calcd for $\text{C}_{21}\text{H}_{24}\text{N}_4\text{O}_5$ H_2O : C, 58.60; H, 6.09; N, 13.02. Found: C, 58.34; H, 5.96; N, 12.67.

(3S) 3-{N-[4-(3-Phenylpropyl)imidazole-2-carbonyl]-L-prolinyl}amino-4-oxo-butanoic acid (21d), was isolated (81%) as a colorless glass: mp. 91-94°C; (methanol-diethyl ether); $[\alpha]_D^{25} -68^\circ$ (c 0.25, MeOH); IR (KBr) 3277, 2939, 1784, 1727, 1662, 1606, 1498, 1429; ^1H NMR(CD_3OD) δ 7.29-7.16 (5H, m), 6.92 (s), 6.86 (s), 4.58-4.16 (3H, m), 3.71 (1H, m), 2.75-1.92 (13H, m). Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_5$ H_2O : C, 59.45; H, 6.35; N,

- 152 -

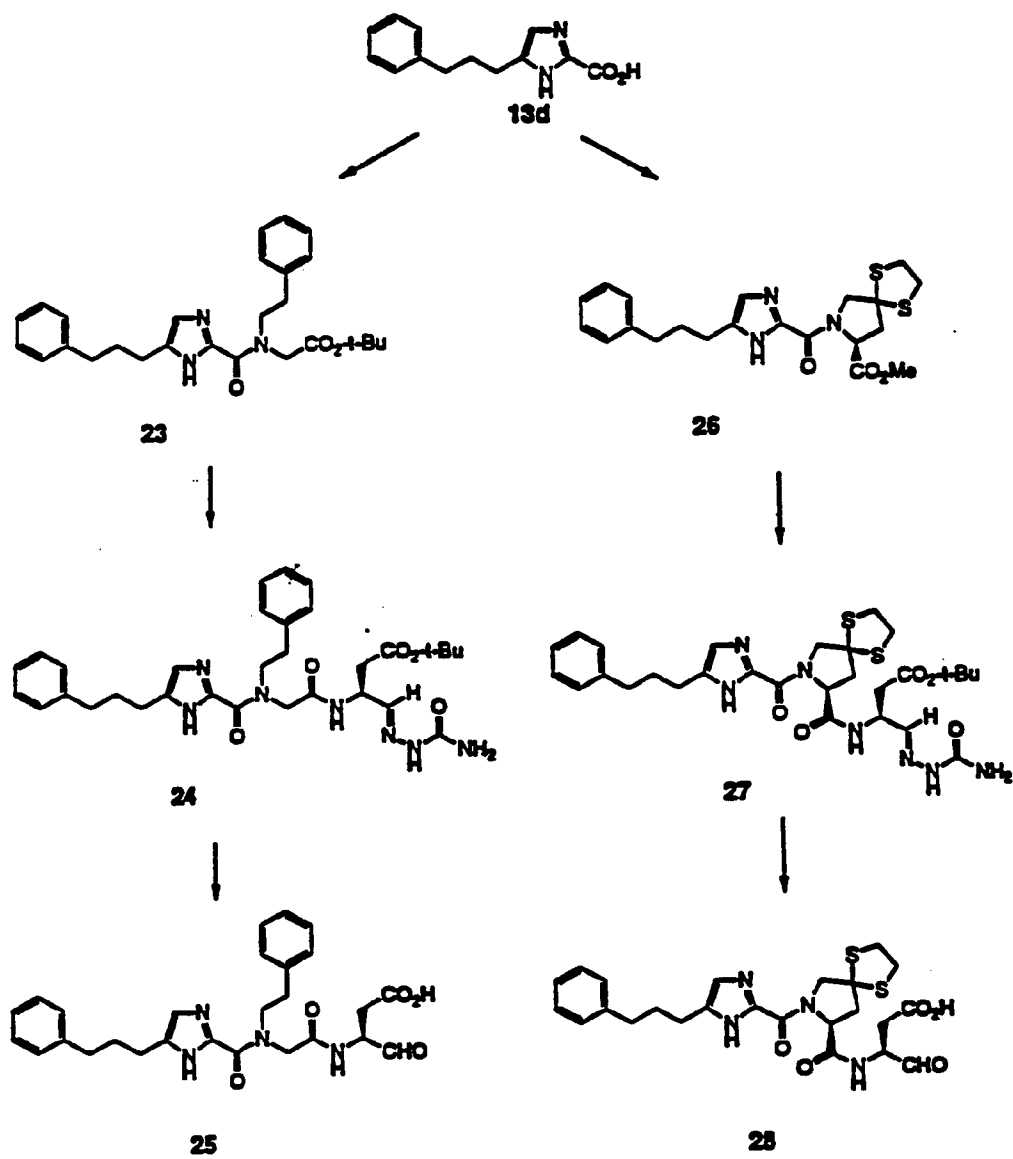
12.60. Found: C, 59.75; H, 6.21; N, 12.41.

(3S) 3-{N-[4-[3-(4-Methoxyphenyl)propyl]imidazole-2-carbonyl]-L-prolinyl}amino-4-oxobutanoic acid (21e),
was isolated (65%) as a white glassy solid: mp. 101-
5 105°C; $[\alpha]_D^{23}$ -60.6 (c 0.05, MeOH); IR (KBr) 3231, 1784,
1726, 1611, 1512, 1245; ^1H NMR(CD_3OD) δ 7.09 (2H, d, $J=8.6$), 6.92, 6.85 (1H, 2 x s), 6.81 (2H, d, $J=8.6$),
5.45-5.30 (1H, m), 4.64-4.46 (1H, m), 4.28-4.10 (2H,
m), 3.75 (3H, s), 3.74-3.66 (1H, m), 2.67-1.84 (13H,
10 m). Anal. Calcd for $\text{C}_{23}\text{H}_{28}\text{N}_4\text{O}_6 \cdot \text{H}_2\text{O}$: C, 58.22; H, 6.37; N, 11.81. Found: C, 58.39; H, 6.34; N, 11.45; FABMS m/e
457 (M^+), 405, 312, 243, 215, 176, 154 (100%).

(3S) 3-{N-[4-[3-(4-Hydroxyphenyl)propyl]imidazole-2-carbonyl]-L-prolinyl}amino-4-oxobutanoic acid (21f),
15 was isolated (43%) as a white glassy solid: mp. 114-
118°C; $[\alpha]_D^{25}$ -55.7° (c 0.05, MeOH); IR (KBr) 3288,
2935, 1780, 1715, 1662, 1610, 1515, 1441; ^1H NMR(CD_3OD)
 δ 6.99 (2H, d, $J=8.5$), 6.91, 6.85 (1H, 2 x s), 6.68
(2H, d, $J=8.5$), 5.45-5.30 (1H, m), 4.60-4.47 (1H, m),
20 4.30-4.10 (2H, m), 3.80-3.55 (1H, m), 2.70-1.80 (13H,
m). Anal. Calcd for $\text{C}_{22}\text{H}_{26}\text{N}_4\text{O}_6 \cdot \text{H}_2\text{O}$: C, 57.38; H, 6.13; N, 12.17. Found: C, 57.68; H, 6.25; N, 11.66. FABMS m/e
443 (M^+), 298, 229, 154 (100%).

3(S)-[(1-{5-[3-(4-Methoxyphenyl)propyl]-1H-imidazole-2-carbonyl}-4(R)-phenoxy pyrrolidine-2(S)-
25 carbonyl)amino]-4-oxobutanoic acid (22e) was isolated
(43%) as a beige solid: ^1H NMR (CD_3OD) δ 7.35-7.2
(3H,m), 7.15-7.0 (2H,m), 6.98-6.85 (3H, m), 6.83-6.77
(2H,d), 5.4-5.1 (1H,m), 4.65-4.5 (1H,m), 4.35-4.2
30 (2H,m), 4.15-3.90 (1H,m), 3.78 (3H, s), 3.62-3.48 (1H,
m), 2.78-2.25 (8H, m), 2.02-1.9 (2H,m).

- 153 -



- 154 -

{Phenethyl-[5-(3-propyl)-1H-imidazole-2-carbonyl]amino}acetic acid tert-butyl ester (23).

A 0°C solution of 4-(3-phenylpropyl)-imidazole-2-carboxylic (13d) (150mg, 0.65mmol) and N-(2-phenethyl)glycine tert-butyl ester (140 mg, 0.59 mmol) in 5 ml of anhydrous dimethylformamide was treated with diisopropylethylamine (154µl, 0.89mmol), hydroxybenzotriazole (160 mg, 1.18 mmol), and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (136 mg, 0.71 mmol). After stirring for 36 h, the reaction was poured onto saturated aqueous sodium chloride and extracted with ethyl acetate (3 x 50ml). The combined organic extracts were washed twice with saturated aqueous sodium bicarbonate (2x) and saturated aqueous sodium chloride (1x), dried (Na₂SO₄), filtered, and concentrated in vacuo to give a brown oil. Chromatography (flash, SiO₂, 30% ethyl acetate/hexane) to give 160mg (61%) of 23 as a white solid: ¹H NMR (CDCl₃) δ 7.38-7.14 (10H, m), 6.85-6.8 (1H, m), 4.84-4.76 (1H, d), 4.5-4.42 (1H, m), 4.07-4.0 (1H, d), 3.78-3.72 (1H, m), 3.12-2.94 (2H, 2 x m), 2.75-2.55 (4H, m), 2.1-1.95 (2H, m), 1.5-1.45 (9H, 3 x s).

(3S)-(2-Phenethyl-[5-(3-phenylpropyl)-1H-imidazole-2-carbonyl]amino)acetyl amino) 4-oxobutanoic acid tert-butyl ester semicarbazone (24). The ester 23 (160mg, 0.357mmol) was treated with 25% trifluoroacetic acid/dichloromethane (7ml) for 4 h. The reaction was concentrated in vacuo to afford 180mg of the acid. The acid (180 mg, 0.357mmol) was coupled to (3S)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (161mg, 0.357mmol) as describe for the preparation of 5a and 5b to give 86 mg (33%) of 24 (one diastereomer) as a white solid : ¹H NMR (CDCl₃) δ 10.9-10.3 (1H, 2 d), 10.08-9.78 (1H, 2 d), 9.25-9.15 (1H, m), 8.35-8.10 (1H, 2 m),

- 155 -

7.9-7.85 (1H, 2 s), 7.40-7.05 (10H, m), 6.9-6.75 (1H,m), 6.3-5.8 (1H, br s), 5.2-4.65 (2H,m), 4.35-3.5 (3H,m), 3.25-3.0 (2H, m), 2.9-2.45 (6H,m), 2.05-1.8 (2H,m), 1.4 (9H,s).

5 **(3S) - (2-{Phenethyl-[5-(3-phenylpropyl)-1H-imidazole-2-carbonyl]amino}acetyl amino)-4-oxobutanoic acid trifluoroacetic acid salt (25)** was prepared by the method described for 7a to afford 32 mg (82%) as a white solid: ¹H NMR (CD₃OD) δ 7.05-7.35 (m, 11H), 4.65
10 (m, 1H), 4.4 (m, 1H), 4.3 (s, 2H), 3.6-4.0 (m, 2H), 2.5-2.95 (m, 8H), 2.05 (m, 2H).

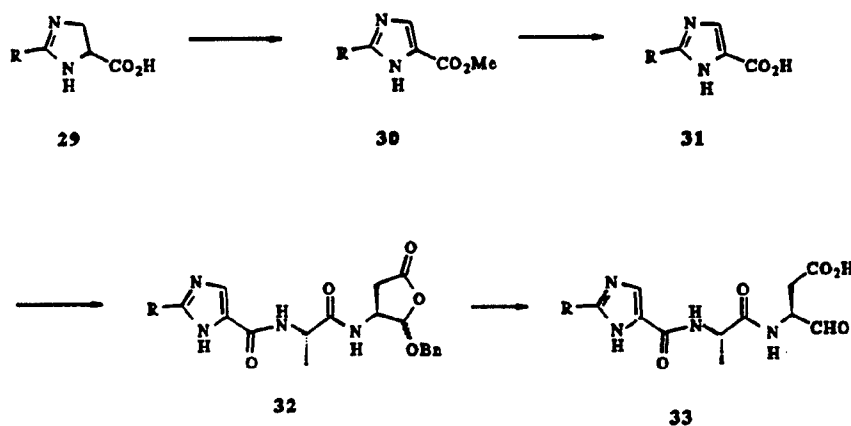
7-[5-(3-Phenylpropyl)-1H-imidazole-2-carbonyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid methyl ester (26). 4-(3-Phenylpropyl)imidazole-2-
15 carboxylic acid (13d) was coupled to 1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carboxylic acid methyl ester hydrobromide (Smith et. al., J. Med. Chem., 31, pp. 875-85 (1988)) by the method described for 23 to afford 140 mg (65%) as a yellow gum: ¹H NMR (CDCl₃) δ 7.34-
20 7.15 (5H, m), 6.98-6.8 (1H, 3 s), 5.7-5.65 (0.5 H, m), 5.2-5.1 (1H,m), 4.82-4.75 (0.5H, m), 4.4-4.35 (1H, m), 4.05 (1H,d), 3.75-3.7 (3H, 2 s), 3.4-3.3 (4H,m), 2.95-2.45 (8H, m), 2.05-1.95 (2H,m).

(3S) - ({7-[5-(3-Phenylpropyl)-1H-imidazole-2-carbonyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carbonyl}-amino)-4-oxobutanoic acid tert-butyl ester semicarbazone (27). Following the procedure described for 4, the ester 26
25 was converted to its acid which was subsequently coupled to (3S)-3-amino-4-oxobutanoic acid tert-butyl ester semicarbazone as described for 24 to give 70 mg
30 (33%) as a brown solid : ¹H NMR (CD₃OD) δ 7.28-7.10 (5H,m), 6.90 (1H, br s), 4.94 (1H, m), 3.96-3.86

- 156 -

(2H,q), 3.35-3.25 (4H,d), 3.0 (2H, s), 2.73-2.59 (6H, m), 2.0-1.92 (2H, m), 1.44 (9H,s).

(3S)-({7-[5-(3-Phenylpropyl)-1H-imidazole-2-carbonyl]-1,4-dithia-7-azaspiro[4.4]nonane-8(S)-carbonyl}-amino)-4-oxobutanoic acid (28) was prepared by the method described for 7a to afford 17 mg (26%) as a light brown solid: ¹H NMR (CD₃OD) δ 7.4 (s, 1H), 7.1-7.25 (m, 5H), 4.9 (m, 1H), 4.6 (m, 1H), 4.3 (m, 1H), 3.95 (s, 2H), 3.25-3.4 (m, 4H), 3.0 (d, 2H), 2.6-2.8 (m, 5H), 2.45 (m, 1H), 2.05 (m, 2H).



- a R = Ph(CH₂)₂
 b R = 4CF₃-Ph(CH₂)₂
 c R = PhCH₂

4,5-Dihydroimidazole-4-carboxylic esters (29) were prepared by a modification of the procedure described by Jones et al., Tetrahedron Lett., 29, pp. 3853-56 (1988).

(4R,S) Methyl 2-(2-phenylethyl)-4,5-dihydroimidazole-4-carboxylate (29a). Dry hydrogen chloride was bubbled

- 157 -

into a solution of hydrocinnamionitrile (3.28ml, 25mmol) in methanol (125ml) at 0°C for 45 mins. The solvents were removed to give the imidate salt which was dissolved in methanol (125ml) along with methyl 2,3-diaminopropionate (25mmol) (Jones et al., *supra*). The mixture was kept at room temperature for 2.5h, then concentrated to a yellow oil. The crude product was purified by column chromatography (10-20% methanol/dichloromethane) to afford 3.52g (61%) of a colorless glass: ¹H NMR(CDCl₃) δ 7.30-7.15 (5H, m), 4.63 (1H, t, J=9.7), 3.96 (2H, d, J=9.7), 3.72 (3H, s), 3.10 (4H, m), ¹³C NMR(CDCl₃) δ 171.3, 168.8, 138.3, 128.4, 128.2, 126.6, 57.3, 53.0, 47.7, 31.7, 27.9.

(4R,S) Methyl 2-[2-(4-trifluoromethylphenyl)ethyl]-4,5-dihydroimidazole-4-carboxylate (29b), was prepared by the method described for 29a to yield 6.80g (78%) of a colorless solid: mp. 136-141°C; ¹H NMR(CDCl₃) δ 7.45 (4H, s), 4.71 (1H, dd, J=8.6,10.8), 4.02 (2H, m), 3.73 (3H, s), 3.19 (4H, m).

Imidazole-4-carboxylic esters 30 were prepared by a modification of the procedure described by Martin et al., *J. Org. Chem.*, 33, pp. 3758-61 (1968).

Methyl 2-(2-phenylethyl)imidazole-4-carboxylate (30a). A mixture of (4R,S) methyl 2-(2-phenylethyl)-4,5-dihydroimidazole-4-carboxylate (29a) (3.40g, 14.64mmol), chloroform (75ml) and manganese (IV) oxide (13.0g, 150mmol) was heated under reflux for 21h then filtered hot. The solids were washed with chloroform and methanol. The combined filtrates were concentrated to leave a yellow-brown solid, which was purified by column chromatography (2-5% methanol/dichloromethane) to afford 1.46g (43%) of a pale yellow solid: mp. 151-

- 158 -

155°C; IR (KBr) 3028, 2946, 1720, 1533, 1433, 1348, 1195, 1166; ¹H NMR(CDCl₃) δ 7.62 (1H, s), 7.26-7.02 (5H, m), 3.82 (3H, s), 3.03 (4H, brs), ¹³C NMR(CDCl₃) δ 162.9, 150.2, 140.3, 128.5, 128.2, 126.3, 51.5, 34.5, 30.4. Anal. Calcd for C₁₃H₁₄N₂O₂ : C, 67.81; H, 6.13; N, 12.16. Found: C, 67.70; H, 6.15; N, 12.16.

Methyl 2-[2-(4-trifluoromethylphenyl)ethyl]imidazole-4-carboxylate (30b), was prepared by the method described for 30a. It was recrystallised from ethyl acetate to afford 1.88g (33%) of cream crystals: mp. 225-26°C; IR (KBr) 3239, 2951, 1715, 1532, 1331, 1158, 1105, 1068; ¹H NMR (CDCl₃) δ 7.61 (1H, s), 7.54 (2H, d, *J* = 8.1), 7.26 (2H, d, *J* = 8.1), 3.89 (3H, s), 3.10 (4H, m). Anal. Calcd for C₁₄H₁₃F₃N₂O₂: C, 56.38; H, 4.39; N, 9.39; F, 19.11. Found: C, 56.23; H, 4.44; N, 9.33; F, 19.08.

2-(2-Phenylethyl)imidazole-4-carboxylic acid (31a). A mixture of methyl 2-(2-phenylethyl)imidazole-4-carboxylate (31a) (1.38g, 6mmol), methanol (30ml) and 1M aqueous sodium hydroxide (30ml) was heated under reflux for 16h. The methanol was removed under reduced pressure, and the resulting aqueous solution was neutralized with 4M hydrochloric acid, whereupon a pale yellow solid precipitated. The precipitate was collected, washed with water, and dried to afford 1.18g (91%) of a pale yellow solid: mp. 117-120°C; IR (KBr) 3375, 3131, 2616, 2472, 1638, 1592, 1551, 1421, 1388, 1360; ¹H NMR(d₆-DMSO) δ 7.59 (1H, s), 7.26 (5H, m), 2.99 (4H, m). Anal. Calcd for C₁₂H₁₂N₂O₂ · 0.25H₂O: C, 65.29; H, 5.71; N, 12.69. Found: C, 65.00; H, 5.64; N, 12.58.

2-[2-(4-Trifluoromethylphenyl)ethyl]imidazole-4-carboxylic acid (31b), was prepared by the method described for 31a to afford 1.09g (76%) of a pale

- 159 -

yellow solid: mp. 126-130°C; IR (KBr) 3339, 2640-2467, 1638, 1589, 1545, 1383, 1323; ¹H NMR(d₆-DMSO) δ 7.69 (2H, d, J=8.0), 7.59 (1H, s), 7.47 (2H, d, J=8.0), 3.06 (4H, m).

5 (2*R,S*, 3*S*) N²-[2-(2-Phenylethyl)imidazole-4-carbonyl]-N-(tetrahydro-2-benzyl-oxy-5-oxo-3-furanyl)-L-alaninamide (32a). To a solution of (2*R,S*, 3*S*) N²-tert-butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (14) (1.59g, 4.20mmol; Chapman, 10 Biorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) in dichloromethane (15ml), cooled to 0°C, was added trifluoroacetic acid (15ml). The mixture was stirred at 0°C for 1h and then concentrated. The residue was treated with ether and then the ether was removed under 15 vacuum. This procedure was repeated twice to yield a pale yellow glass. The solid was dissolved in DMF (20ml), then diisopropylethylamine (2.19ml, 12.6mmol), 2-(2-phenylethyl)imidazole-4-carboxylic acid (31a) (1.0g, 4.62mmol), 1-(3-dimethylaminopropyl)-3-ethyl 20 carbodiimide hydrochloride (0.89g, 4.62mmol) and hydroxybenzotriazole (1.14g, 8.40mmol) were added to the solution. The reaction mixture was stirred at room temperature for 20h then poured into brine. The mixture was extracted with ethyl acetate (3 x 50ml). 25 The combined organic extracts were washed with saturated aqueous sodium bicarbonate (3 x 100ml) then brine (3 x 100ml), dried (MgSO₄) and concentrated. The residue was purified by column chromatography (2-10% isopropanol in dichloromethane then 0-6% isopropanol in 30 ethyl acetate) to yield 1.10g (55%) of 32a as a mixture of diastereomers: IR (KBr) 3278, 3065, 1790, 1641, 1577, 1545, 1499, 1454, 1120; ¹H NMR(CDCl₃) δ 10.26 (1H, s), 8.14 (1H, s), 7.66 (d, J=7.0), 7.56 (d, J=7.0), 7.43 (1H, s), 7.31-7.11 (10H, m), 5.49 (d, J=5.6), 5.48

- 160 -

(s), 4.83-4.41 (4H, m), 3.04-2.41 (2H, m), 2.99 (4H, s), 1.45 (d, $J=7.0$), 1.44 (d, $J=7.0$).

(2*R,S*, 3*S*) N^2 -{2-[2-(4-Trifluoromethylphenyl)ethyl]imidazole-4-carbonyl}-*N*-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-*L*-alaninamide (32b), was prepared by the method described for 32a to afford 1.08g (62%) of a pale yellow glass: IR (KBr) 3376, 3284, 3070, 2938, 1791, 1642, 1578, 1546, 1327, 1165, 1122, 1068; ^1H NMR(CDCl_3) δ 7.95 (0.5H, m), 7.55-7.25 (11.5H, m), 5.53 (s), 5.49 (d, $J=5.3$), 4.88-4.48 (4H, m), 3.11-2.96 (4H, m), 2.91 (1H, m), 2.51 (1H, m), 1.47 (3H, d, $J=7.1$).

(2*R,S*, 3*S*) N^2 -(2-Benzylimidazole-4-carbonyl)-*N*-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-*L*-alaninamide (32c), was prepared by the method described for 32a from 2-benzylimidazole-4-carboxylic acid (Ger. Offen. DE 3427136) to afford 1.13g (83%) of a yellow glass: IR (CH_2Cl_2) 3433, 3062, 2990, 1803, 1693, 1584, 1504, 1429, 1285, 1258; ^1H NMR(CDCl_3) δ 9.50 (s), 9.37 (s), 7.86 (0.5H, d, $J=6.1$), 7.56-7.21 (10.5H, m), 7.48 (1H, s), 5.51 (d, $J=5.2$), 5.48 (s), 4.87-4.41 (4H, m), 4.08 (s), 4.07 (s), 3.03-2.39 (2H, m), 1.46 (3H, d, $J=7.0$).

(3*S*) 3-{*N*-[2-(2-Phenylethyl)imidazole-4-carbonyl]-*L*-alaninyl}amino-4-oxobutanoic acid (33a; **A**). A mixture of (2*R,S*, 3*S*) N^2 -[2-(2-phenylethyl)imidazole-4-carbonyl]-*N*-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-*L*-alaninamide (32a) (1.0g, 2.10mmol) and 10% palladium on activated carbon (1.0g) in methanol (50ml) was stirred under a hydrogen atmosphere for 4.5h. The resulting mixture was filtered and concentrated to yield a colorless glass. Recrystallization from methanol-diethyl ether afforded 510mg (63%) of a colorless

- 161 -

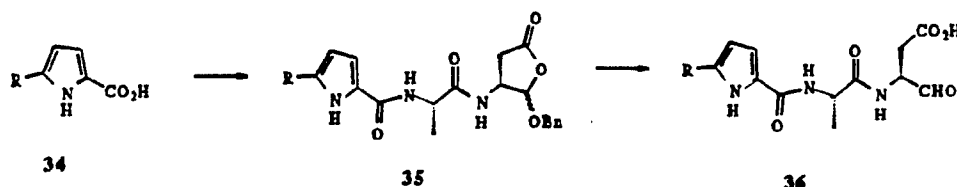
solid: mp. 127°C; IR (KBr) 3360, 3279, 2981, 1781, 1732, 1646, 1577, 1547; ¹H NMR (CD₃OD) δ 7.54 (1H, s), 7.29-7.12 (5H, m), 4.60-4.47 (2H, m), 4.28 (1H, m), 3.01 (4H, s), 2.76-2.39 (2H, m), 1.43 (3H, 2 x d, J=7.0, J=7.0), ¹³C NMR (CD₃OD) δ 176.2, 176.0, 174.7, 174.6, 164.4, 164.3, 150.5, 141.9, 134.8, 129.5, 129.3, 127.3, 122.3, 98.8, 98.4, 52.3, 52.0, 50.3, 35.6, 31.2, 18.8, 18.7. Anal. Calcd for C₁₉H₂₂N₄O₅ · H₂O: C, 56.43; H, 5.98; N, 13.85. Found: C, 56.78; H, 5.70; N, 13.77.

10 (3S) 3-{N-[2-(2-[4-Trifluoromethylphenyl]ethyl)imidazole-4-carbonyl]-L-alaninyl}-amino-4-oxobutanoic acid (33b; **C**), was prepared by the method described for 33a to afford 612mg (73%) of a colorless solid: mp. 120-124°C; [α]_D²³ +14.3° (c 0.5, MeOH); IR (KBr) 3287, 2985, 2937, 1782, 1732, 1646, 1579, 1547, 1327; ¹H NMR (CD₃OD) δ 7.56 (2H, d, J=8.0), 7.54 (1H, s), 7.36 (2H, d, J=8.0), 4.60-4.48 (2H, m), 4.28 (1H, m), 3.08 (4H, m), 2.75-2.41 (2H, m), 1.43 (3H, d, J=7.0). Anal. Calcd for C₂₀H₂₁F₃N₄O₅ · 0.5H₂O : C, 51.84; H, 4.78; N, 12.09; F, 12.30. Found: C, 51.83; H, 4.72; N, 12.14; F, 12.36.

(3S) 3-[N-(2-Benzylimidazole-4-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (33c; **B**), was prepared by the method described for 33a to afford 25 426mg (64%) of a colorless solid: [α]_D²³ +13.4° (c 0.407, MeOH). IR (KBr) 3260, 3150, 2980, 1779, 1727, 1649, 1573, 1547; ¹H NMR (CD₃OD) δ 7.58 (1H, s), 7.34-7.22 (5H, m), 4.59-4.47 (2H, m), 4.28 (1H, m), 4.07 (2H, s), 2.74-2.41 (2H, m), 1.42 (3H, d, J=6.7); ¹³C NMR (CD₃OD) δ 175.6, 175.5, 175.0, 164.6, 164.5, 150.1, 30 138.7, 135.3, 130.0, 129.9, 128.2, 122.9, 98.9, 98.5, 52.5, 52.2, 35.5, 35.1, 35.0, 19.0, 18.9. Anal. Calcd for C₁₈H₂₀N₄O₅ · H₂O: C, 55.37; H, 5.68; N, 14.35. Found C,

- 162 -

55.83; H, 5.75; N, 13.96. MS(FAB, m/z) : 373 (M^+), 228, 185, 91.



(a) R = H
(b) R = CH₂Ph

- 5 **5-Benzylpyrrole-2-carboxylic acid (34b).** A mixture of Ethyl 5-benzylpyrrole-2-carboxylate (0.7g, 3.05mmol; Elder et al., Synthetic Communications, 19, 763-767 (1989)), ethanol (20ml) and 1M sodium hydroxide (9.2ml, 9.2mmol) was stirred and heated under reflux for 3h.
- 10 The major part of the ethanol was removed and the remaining liquid was diluted with water, washed with ether, cooled in ice and acidified with concentrated hydrochloric acid. The mixture was extracted with ether. The combined extracts were washed with brine,
- 15 dried (Na₂SO₄) and concentrated to afford 0.567g (92%) of an off white solid: mp. 130-134°C; ¹H NMR(CDCl₃) δ 8.87 (1H, brs), 7.37-6.95 (5H, m), 6.97 (1H, m), 6.07 (1H, m), 4.00 (2H, s).

- 20 **(2R,S, 3S) N²-(Pyrrole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (35a).** A solution of (2R,S, 3S) N²-tert-butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (14) (756mg, 2.0mmol) in dry dichloromethane (8ml) at 0°C was treated with trifluoroacetic acid (8ml) for 1h
- 25 and then evaporated to dryness. Dry ether was added to the residue and the mixture concentrated to give a viscous oil. The oil was dissolved in dry DMF (10ml).

- 163 -

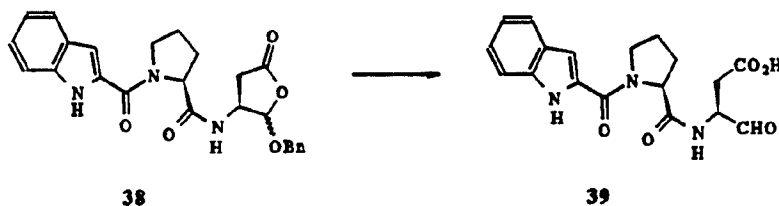
Pyrrole-2-carboxylic acid (**34a**) (244mg, 2.2mmol) was added and the solution was cooled in an ice bath before the addition of N,N-diisopropylamine (0.78g, 6.0mmol), 1-hydroxybenzotriazole (0.54g, 4.0mmol) and ethyl dimethylaminopropyl carbodiimide hydrochloride (0.42g, 2.2mmol). The resulting mixture was stirred at 25°C for 17h and then saturated aqueous sodium chloride (30ml) was added. The mixture was extracted with ethyl acetate (3 x 20ml) and the combined organic extracts were washed with 5% aqueous sodium bicarbonate (3 x 10ml) and brine (10ml), dried (MgSO₄) and concentrated. Flash chromatography (25% hexane-ethyl acetate) afforded 557mg (75%) of a 1:1 mixture of diastereomers as a white glassy solid: mp. 85-90°C; IR (KBr) 3288, 1789, 1665, 1629, 1557 and 1122; ¹H NMR(d₆-DMSO) δ 11.46 (1H, bs), 8.55 (0.5H, d, J=7.0), 8.30 (0.5H, d, J=7.6), 8.06 (0.5H, d, J=7.0), 8.04 (0.5H, d, J=7.6), 7.36-7.30 (5H, m), 6.88-6.85 (2H, m), 6.10-6.07 (1H, m), 5.63 (0.5H, d, J=5.0), 5.42 (0.5H, s), 4.72 (2H, q, J=12.2), 4.74-4.25 (2H, m), 3.14-2.35 (2H, m), 1.29, 1.25 (3H, 2 x d, J=7.2).

(2*R,S*, 3*S*) N²-(5-Benzylpyrrole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-alaninamide (**35b**), was prepared from 5-benzylpyrrole-2-carboxylic acid (**34b**) by the method described for compound **35a** (65%). Data is given for a single diastereomer. ¹H NMR (d₆-DMSO) δ 11.37 (1H, brs), 8.27 (1H, d, J=7.4), 7.93 (1H, d, J=7.6), 7.33-7.16 (10H, m), 6.76 (1H, m), 5.82 (1H, m), 5.62 (1H, d, J=5.2), 4.76 (1H, d, J=12.0), 4.65 (1H, m), 4.62 (1H, d, J=12.2), 4.47 (1H, m), 3.88 (2H, s), 2.77 (1H, dd, J=9.0,18.0), 2.5 (dd), 1.23 (3H, d, J=7.0).

- 164 -

(3S) 3-[N-(Pyrrole-2-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (36a; **D**). A mixture of (35a) (612mg; 1.65mmol), methanol (40ml) and 10% palladium on carbon (500mg) was vigorously stirred under an atmosphere of hydrogen for 4h. The mixture was filtered through a 0.2 μ M nylon membrane then concentrated. The residue was purified by flash chromatography (5-10% methanol in methylene chloride) to afford the hemihydrate of (36a) (223mg, 48%) as a white solid after precipitation from an ethyl acetate-ether mixture. There were traces of solvent in the product: mp. 96-100°C; IR (KBr) 3381, 1774, 1729 (EtOAc), 1632, 1558, 1523, 1123; ¹H NMR(CD₃OD) δ 6.94-6.85 (2H, m), 6.17 (1H, dd, *J*=3.8 and 2.6), 4.58 (0.5H, d, *J*=3.94), 4.56 (0.5H, d, *J*=4.24), 4.51 (1H, q, *J*=7.16), 4.35-4.20 (1H, m), 2.74-2.40 (2H, m), 1.42 and 1.41 (3H, 2 x d, *J*=7.13).

(3S) 3-[N-(5-Benzylpyrrole-2-carbonyl)-L-alaninyl]amino-4-oxobutanoic acid (36b), was prepared (41%) from 35b by the method described for compound 36a, to afford an off white solid: mp. 109-112°C; [α]_D²⁵ +6.3° (c 0.3, methanol); IR (KBr) 3368, 1724, 1630, 1530, 1453, 1414, 1233, 1049; ¹H NMR(d₄ methanol) δ 7.25-7.11 (5H, m), 6.76 (1H, d, *J*=3.5), 5.84 (1H, d, *J*=3.5), 4.51 (1H, m), 4.43 (1H, q, *J*=7.1), 4.23 (1H, m), 2.5 (2H, m), 1.35 (3H, d, *J*=7.0). Anal. Calcd for C₁₉H₂₁N₃O₅ · 1.75 H₂O: C, 56.64; H, 6.13; N, 10.43. Found: C, 56.34; H, 5.72; N, 10.00.



- 165 -

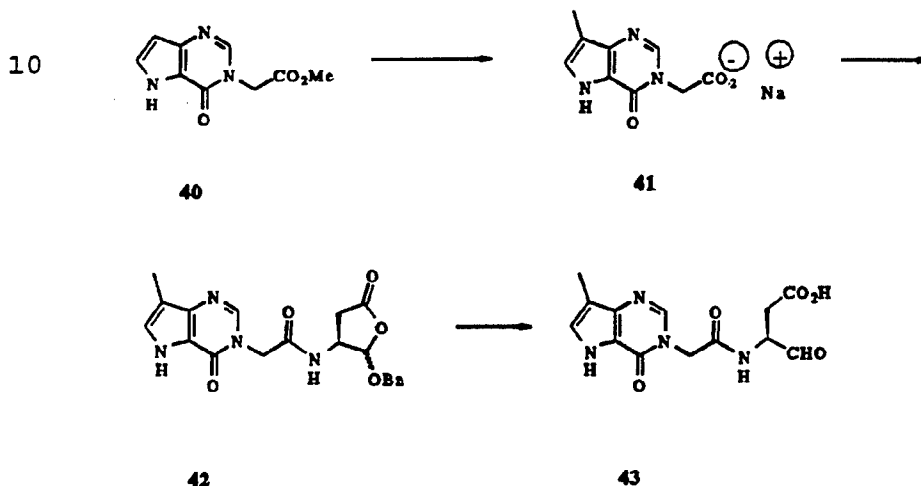
(2*R,S*, 3*S*) 1-(Indole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-prolinamide (38).

Trifluoroacetic acid (4ml) was added to a solution of (2*R,S*, 3*S*) 1-tert-butoxycarbonyl-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-prolinamide (15) (0.607g, 1.5mmol) in dichloromethane (4ml) at 0°C. The mixture was stirred at 0°C for 75 min. The mixture was concentrated, and the residue treated with diethyl ether, then the ether was removed under vacuum. This procedure was repeated twice to yield a yellow oil, which was dissolved in DMF (12ml). Diisopropylethylamine (0.78ml, 4.5mmol) followed by indole-2-carboxylic acid (266mg, 1.65mmol), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (316mg, 1.65mmol) and hydroxybenzotriazole (405mg, 3mmol) were then added to the solution. The mixture was stirred at room temperature for 20h then poured into brine. The mixture was extracted with ethyl acetate (3 x 30ml). The combined organic extracts were washed with saturated aqueous sodium bicarbonate (2 x 60ml) then brine (2 x 60ml), dried (MgSO₄), filtered and concentrated. The residue was purified by column chromatography (ethyl acetate) to afford 518mg (77%) of a mixture of diastereomers: IR (KBr) 3314, 1780, 1677, 1609, 1524, 1435, 1406, 1344; ¹H NMR (d₆-DMSO), δ 11.58 (1H, m), 8.81-8.41 (1H, m), 7.71-6.67 (10H, m), 5.70 (d, J=5.2), 5.48 (s), 4.89-4.29 (4H, m), 3.99-3.74 (2H, m), 3.20-2.44 (2H, m), 2.39-1.77 (4H, m).

(3*S*) 3-[1-(Indole-2-carbonyl)-L-prolinyl]amino-4-oxobutanoic acid (39). A mixture of (2*R,S*, 3*S*) 1-(indole-2-carbonyl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)-L-prolinamide (38) (478mg, 1.07mmol) and 10% palladium on carbon (475mg) and methanol (150ml) was stirred under a hydrogen atmosphere for 6h. The

- 166 -

resulting mixture was filtered and concentrated to yield a colorless glass. Recrystallization from a mixture of methanol and diethyl ether afforded 202mg (53%) of a colorless solid: mp. 135-138°C; $[\alpha]_D^{24}$ -44° (c 0.25, CH₃OH); IR (KBr) 3287, 2977, 2879, 1781, 1725, 1716, 1667, 1662, 1600, 1529, 1441, 1346; ¹H NMR(CD₃OD) δ 7.65 (1H, d, J=8.0), 7.44 (1H, d, J=8.4), 7.22 (1H, m), 7.09-6.84 (2H, m), 4.62 (2H, m), 4.29 (1H, m), 4.15-3.73 (2H, m), 2.74-1.72 (6H, m).



Methyl 2-(3,5-dihydro-7-methyl-4-oxo-4H-pyrrolo [3,2-d] pyrimidin-3-yl)acetate (40). Freshly prepared methyl glycinate (1.25g, 14mmol) was added to a stirred solution of ethyl 3-[N-(dimethylamino) methylene]amino-4-methylpyrrole-2-carboxylate (1.56g, 7.0mmol; Lim et al., J. Org. Chem., 44, pp. 3826-29 (1979)) in dry methanol (60ml). The resulting mixture was kept at 70°C. Two further batches of methyl glycinate (1.25, 14.0mmol) were added after 18h and 42h heating. The mixture was cooled and filtered 24h after the final addition. The filtrate was concentrated and the residue purified by flash chromatography (2-5%

- 167 -

methanol/chloroform) to afford 0.54g (35%) of a white crystalline solid: mp. 233-235°C (recrystallized from ethyl acetate); IR (KBr) 3135, 2958, 1745, 1675, 1254; ¹H NMR (d₆-DMSO) δ 11.90 (1H, s), 8.07 (1H, s), 7.23 (1H, s), 4.83 (2H, s), 3.69 (3H, s), 2.16 (3H, s).
Anal. Calcd for C₁₀H₁₁N₃O₃ · 0.1H₂O: C, 53.85; H, 5.07; N, 18.84. Found: C, 53.85; H, 4.96; N, 18.81;
MS(70eV.E.I.) m/e 222, 221 (M⁺, 100%), 189, 162, 133, 105.

10 **2-(3,5-Dihydro-7-methyl-4-oxo-4H-pyrrolo[3,2-d]pyrimidin-3-yl)acetic acid, sodium salt (41).** A suspension of 40 (354mg, 1.6mmol) in methanol (15ml) was treated with 0.5N sodium hydroxide (4.8ml) and the resulting mixture was stirred at 25°C for 1h. The
15 reaction mixture was filtered to afford the hemihydrate of 41 (354mg, 97%) as a white crystalline solid : mp. >340°C (recrystallized from methanol); IR (KBr) 3461, 3143, 1676, 1666, 1605, 1415; ¹H NMR(d₆ DMSO) δ 11.63 (1H, s), 7.83 (1H, s), 7.11 (1H, d, J=2.0), 4.24 (2H, s), 2.14 (3H, s).
20 Anal. Calcd for C₉H₈N₃O₃Na · 0.5H₂O: C, 45.39; H, 3.81; N, 17.64. Found: C, 45.57; H, 4.05; N, 17.39.

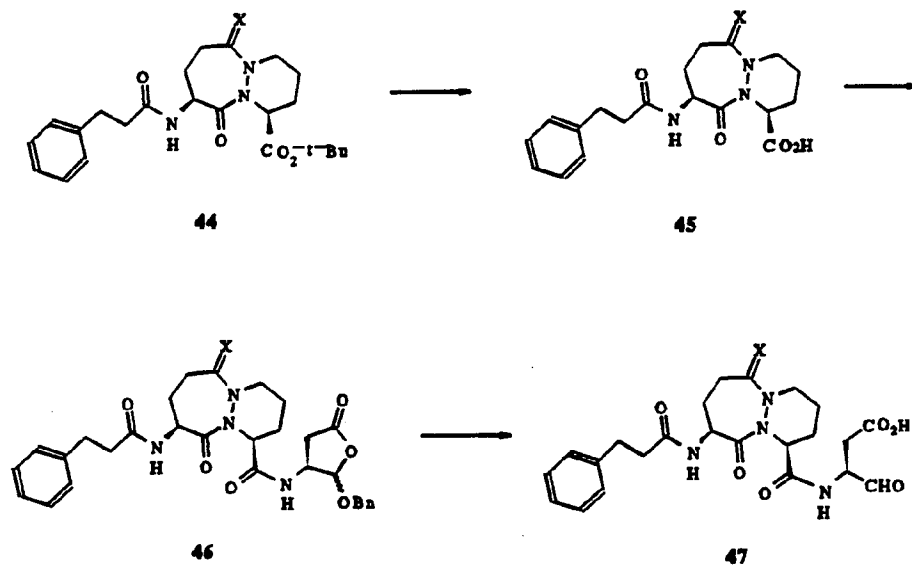
(2*R,S*, 3*S*) **2-(3,5-Dihydro-7-methyl-4-oxo-4H-pyrrolo[3,2-d]pyrimidin-3-yl)-N-(tetrahydro-2-benzyloxy-5-oxo-3-furanyl)acetamide (42).** A suspension
25 of the sodium salt 41 (344mg, 1.5mmol) in dry DMF (15ml) was treated with ethyl dimethylaminopropyl carbodiimide hydrochloride (373mg, 1.95mmol) and 1-hydroxybenzo-triazole (405mg, 3.0mmol). The mixture
30 was kept at 25°C for 1h then (2*R,S*, 3*S*) N-allyloxycarbonyl-3-amino-2-benzyloxy-5-oxotetrahydrofuran (437mg, 1.5mmol; Chapman, Biorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) and (Ph₃P)₂PdCl₂

- 168 -

(25mg) were added followed by the dropwise addition of n-tributyltin hydride (0.6ml, 2.25mmol). The resulting mixture was stirred at 25°C for 1h then water (20ml) was added. The mixture was extracted with ethyl acetate (3 x 15ml), and the combined organic extracts were washed with water (5ml), dried (MgSO₄), and concentrated to afford a mixture of diastereomers. Evaporation of the aqueous phase and purification of the residue by flash chromatography (5% methanol/chloroform) gave an additional quantity affording a total 182mg of **42** (31%) : m.p. 240-244°C; IR (KBr) 3274, 1772, 1691, 1664, 1562; ¹H NMR (d₆-DMSO) δ 11.81 (1H, s), 8.85 (0.6H, d, J=6.6), 8.72 (0.4H, d, J=7.4), 7.98 (0.6H, s), 7.95 (0.4H, s), 7.40-7.30 (5H, m), 7.20 (1H, d, J=2.2), 5.61 (0.4H, d, J=5.0), 5.46 (s), 4.85-4.60 (m), 4.28 (m), 3.20-2.35 (2H, m), 2.16 (3H, s).

(3*S*)-3-[2-(3,5-Dihydro-7-methyl-4-oxo-4H-pyrrolo[3,2-d]pyrimidin-3-yl)-1-oxo-ethylamino]-4-oxobutanoic acid (**43**). A mixture of **42** (131mg, 0.33mmol), in methanol (50ml) and 10% palladium on carbon (100mg) was stirred vigorously under an atmosphere of hydrogen for 2h. An additional quantity of catalyst (100mg) was added and the mixture hydrogenated for a further 2h. The mixture was filtered through a 0.2μM nylon membrane, and concentrated. The residue was recrystallized from methanol/diethyl ether to afford 79mg (78%) of **43** as a hygroscopic white solid: mp. 222-226°C; (decomp.); [α]_D³² +0.5 (c 0.02, MeOH); IR (KBr) 3282, 1680, 1558, 1425 1275; ¹H NMR (CD₃OD) δ 8.03 (1H, s), 7.18 (1H, d, J=0.7), 4.79-4.74 (2H, m), 4.63-4.59 (1H, 2 x d, J=3.6), 4.36-4.25 (1H, m), 2.78-2.39 (2H, m), 2.24 (3H, d, J=0.7). Anal. Calcd for C₁₃H₁₄N₄O₅ · 1.4H₂O: C, 47.10; H, 5.12; N, 16.90. Found: C, 47.00; H, 4.79; N, 16.59.

- 169 -

FABMS m/e 307, 306 (M⁺), 244, 207, 190, 152, 115 (100%).

- (a) X = O
 (b) X = H₂

5 (1*S*,9*S*) *t*-Butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6*H*-pyridazino[1,2-*a*]
 phenylpropionylamino)-6*H*-pyridazino[1,2-*a*]
 [1,2]diazepine-1-carboxylate (44a). To a solution of
 (1*S*,9*S*)*t*-butyl 9-amino-6,10-dioxo-octahydro-6*H*-
 pyridazino [1,2-*a*] [1,2]diazepine-1-carboxylate (690mg;
 10 2.32mmol; GB 2128984) in dioxane (16ml) and water (4ml)
 at 0°C was added solid sodium bicarbonate (292mg;
 3.48mmol) followed by dropwise addition of 3-
 phenylpropionyl chloride (470mg; 2.78mmol). The
 mixture was stirred at room temperature for 2h then
 15 more sodium bicarbonate (200mg; 2.38mmol) and 3-
 phenylpropionyl chloride (100mg; 0.6mmol) was added.
 The mixture was stirred for a further 2h at room
 temperature, diluted with ethyl acetate (50ml), washed

- 170 -

with saturated sodium bicarbonate (2 x 25ml) then dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (0-50% ethyl acetate/chloroform) and finally crystallized by trituration with ether to afford 860mg (86%) of a white solid: mp. 137-138°C; [α]_D²³ -95.1° (c 0.549, CH₂Cl₂); IR (KBr) 3327, 1736, 1677, 1664, 1536, 1422, 1156; ¹H NMR (CDCl₃) δ 7.24 (5H, m), 6.50 (1H, d, J=7.5), 5.24 (1H, m), 4.90 (1H, m), 4.60 (1H, m), 3.44 (1H, m), 2.93 (2H, m), 2.84 (1H, m), 2.64 (1H, m), 2.54 (2H, m), 2.26 (2H, m), 1.70 (4H, m), 1.70 (9H, s). MS(FAB, m/z): 430 (M⁺ + 1), 374, 242, 105, 91.

(1*S*,9*S*)-t-Butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino-[1,2-a][1,2]diazepine-1-carboxylate (44b), was prepared from (1*S*, 9*S*)-t-butyl 9-amino-octahydro-10-oxo-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (Attwood et al., J. Chem. Soc. Perkin 1, pp. 1011-19 (1986)) as for 44a, to afford 810mg (81%) of a colorless oil: [α]_D²³ - 33.5° (c 0.545, CH₂Cl₂); IR (film) 3334, 2935, 1737, 1728, 1659, 1642; ¹H NMR (CDCl₃) δ 7.24 (5H, m), 6.75 (1H, d, J=6.7), 5.27 (1H, m), 4.92 (1H, m), 3.39 (1H, m), 3.03 (4H, m), 2.55 (3H, m), 2.33 (1H, m), 2.17 (1H, m), 1.80 (5H, m), 1.47 (9H, s), 1.39 (1H, m). MS(FAB, m/z): 416 (M⁺ + 1), 360, 211, 143, 97.

(1*S*,9*S*) 6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylic acid (45a). To a solution of (1*S*,9*S*) t-butyl 6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-a][1,2]diazepine-1-carboxylate (44a) (800mg; 1.863mmol) in dry dichloromethane (5ml) at 0°C was added trifluoroacetic acid (5ml). The solution was stirred

- 171 -

at room temperature for 3h then concentrated. Dry ether (10ml) was added to the residue then removed under vacuum. This process was repeated three times to afford a crystalline solid. The solid was triturated with ether and filtered to afford 590mg (85%) of a white crystalline solid: mp. 196-197.5°C; $[\alpha]_D^{23}$ -129.5° (c 0.2, CH₃OH); IR (KBr) 3237, 1729, 1688, 1660, 1633, 1574, 1432, 1285, 1205; ¹H NMR (CD₃OD) δ 8.28 (1H, d, J=7.4), 7.22 (5H, m), 5.32 (1H, dd, J=5.9, 2.9), 4.75 (1H, m), 4.51 (1H, m), 3.50 (1H, m), 3.01 (1H, m), 2.91 (2H, m), 2.55 (2H, m), 2.29 (3H, m), 1.95 (2H, m), 1.71 (2H, m). Anal. Calcd for C₁₉H₂₃N₃O₅: C, 61.12; H, 6.21; N, 11.25. Found: C, 60.80; H, 6.28; N, 10.97. MS(FAB, m/z) 374 (M⁺ + 1), 242, 105, 91.

(1*S*, 9*S*) Octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-*a*]-[1,2]diazepine-1-carboxylic acid (45b), was prepared from (1*S*, 9*S*) *t*-butyl octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylate (44b) by the method described for compound 45a to afford 657mg (96%) of 45b as a crystalline solid: mp. 198-202°C; $[\alpha]_D^{23}$ -86.2° (c 0.5, CH₃OH); IR (KBr) 3294, 2939, 1729, 1645, 1620, 1574, 1453, 1214; ¹H NMR (CD₃OD) δ 7.92 (1H, d, J=7.9), 7.20 (5H, m), 5.29 (1H, m), 4.90 (1H, m), 3.47 (1H, m), 3.08 (2H, m), 2.90 (2H, m), 2.55 (3H, m), 2.36 (1H, m), 1.81 (5H, m), 1.43 (2H, m). MS(FAB, m/z) 360 (M⁺ +1), 211, 143, 91.

[3*S*, 2*R*, *S*, (1*S*, 9*S*)] *N*-(2-Benzylloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (46a). To a solution of (1*S*, 9*S*) 6,10-dioxo-octahydro-9-(3-phenyl-propionylamino)-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid (45a) (662mg;

- 172 -

1.773mmol) in dry dichloromethane (9ml) and dry dimethyl formamide (3ml) at room temperature was added bis(triphenylphosphine)palladium chloride (30mg) and (3*S*, 2*R*,*S*)-3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (Chapman, Bior. Med. Chem. Lett., 2, pp. 613-18 (1992)) (568mg; 1.95mmol) followed by dropwise addition of tri-*n*-butyltin hydride (1.19g; 4.09mmol). 1-Hydroxy-benzotriazole (479mg; 3.546mmol) was added to the mixture and the mixture was cooled to 0°C before addition of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (408mg; 2.128mmol). The mixture was stirred at room temperature for 3.25h then diluted with ethyl acetate (50ml), washed twice with dilute hydrochloric acid (20ml), twice with saturated sodium bicarbonate (20ml), once with brine then dried (MgSO₄) and concentrated. The resulting oil was purified by flash chromatography (0-100% ethyl acetate/chloroform) to afford 810mg (81%) of **46a** as a mixture of anomers: mp. 92-94°C; IR (KBr) 3311, 1791, 1659, 1651, 1536; ¹H NMR(CDCl₃) δ 7.49, 6.56 (1H, 2d, *J*=6.7, 7.8), 7.29 (10H, m), 6.37, 6.18 (1H, 2d, *J*=7.7, 7.6), 5.56, 5.34 (1H, d, *s*, *J*=5.2), 5.08-4.47 (6H), 3.18-2.80 (5H), 2.62-2.28 (5H), 2.04-1.53 (5H). MS(FAB, *m/z*), 563 (*M*⁺ + 1), 328, 149, 91.

[3*S*, 2*R*,*S*, (1*S*, 9*S*)] N-(2-Benzyloxy-5-oxotetrahydrofuran-3-yl)-octahydro-10-oxo-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (**46b**), was prepared from **45b** by the method described for **46a** to yield 790mg (96%) of a glass: m.p. 58-60°C; IR (KBr) 3316, 2940, 1793, 1678, 1641, 1523, 1453, 1120; ¹H NMR (CDCl₃) δ 7.28 (10H, m), 6.52, 6.42 (1H, 2d, *J*=7.2, 7.1), 5.53, 5.44 (1H, d, *s*, *J*=5.2), 5.35 (1H, m), 4.6-4.9, 4.34 (4H, m), 3.1-2.8 (6H, m), 2.6-2.1 (7H), 1.95-1.05 (5H).

- 173 -

MS (FAB, m/z), 549 ($M^+ + 1$), 400, 310, 279, 91.

[3*S*, (1*S*, 9*S*)] 3-(6,10-Dioxo-octahydro-9-(3-phenylpropionylamino)-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47a).

5 A mixture of [3*S*, 2*R,S*, (1*S*, 9*S*)] *N*-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)-6,10-dioxo-octahydro-9-(3-phenylpropionylamino)-6*H*-pyridazino[1,2-*a*][1,2]diazepine-1-carboxamide (46a) (205mg; 0.364mmol), 10% palladium on carbon (200mg) and methanol (20ml) was
10 stirred under hydrogen at atmospheric pressure for 5h. The mixture was filtered then concentrated to yield 154mg (90%) of a glass: mp. 116-118°C; $[\alpha]_D^{23}$ -140° (c 0.1, CH₃OH); IR (KBr) 3323 (br), 1783, 1731, 1658, 1539, 1455, 1425; ¹H NMR (CD₃OD) δ 7.21 (5H, m), 5.17 (1H, m), 4.73 (1H, m), 4.50 (2H, m), 4.23 (1H, m), 3.38 (1H, m), 3.06 (1H, m), 2.91 (2H, m), 2.73-2.18 (6H, m) and 2.01-1.59 (5H, m). Anal. Calcd for C₂₃H₂₇N₄O₇ + H₂O : C, 56.32; H, 6.16; N, 11.42. Found: C, 56.29; H, 6.11; N, 11.25. MS (FAB, m/z) 473 ($M^+ + 1$), 176, 149, 105, 91.

20 [3*S*, (1*S*, 9*S*)] 3-(Octahydro-10-oxo-9-(3-phenylpropionylamino)-6*H*-pyridazino-[1,2-*a*][1,2]diazepine-1-carboxamido)-4-oxobutanoic acid (47b), was prepared from 46b by the method described for 47a. The residue was purified by flash chromatography (0-10%
25 methanol/chloroform) to afford 65mg (52%) of a glass; m.p. 87-90°C; $[\alpha]_D^{23}$ -167.0° (c 0.1, methanol); IR (KBr) 3329, 2936, 1786, 1727, 1637; ¹H NMR (CD₃OD) δ 7.23 (5H, m), 5.29 (1H, m), 4.83 (1H, m), 4.59 (1H, d, *J*=3.6), 4.29 (1H, m), 3.3-3.0 (3H, m), 2.91 (2H, m),
30 2.70-2.34 (5H, m), 2.19 (2H, m), 1.75 (4H, m), 1.36 (2H, m). Anal. Calcd for C₂₃H₃₀N₄O₆ + 0.5H₂O: C, 59.09; H, 6.68; N, 11.98. Found: C, 58.97; 6.68; N, 11.73. MS (FAB, m/z) 459 ($M^+ + 1$), 310, 149, 105, 91.

- 174 -



	R ₁	R ₂	R ₃
	(a) PhCH ₂	H	(S) Me
	(b) PhCH ₂	CH ₂ Ph	H
5	(c) PhCH ₂	(CH ₂) ₂ Ph	H
	(d) PhCH ₂	nBu	H
	(e) PhCH ₂	Me	H
	(f) PhCH ₂	Ph	H
	(g) PhCH ₂	H	H
10	(h) PhCH ₂	CH ₂ Ph	(S) -Me
	(i) Ph(CH ₂) ₂	CH ₂ Ph	H

Pyridones **48** were prepared by the method described by Damewood et al., J. Med. Chem., 37, pp. 3303-12 (1994)). Compound **48d** is new.

15 **3-Benzyloxycarbonylamino-6-butyl-pyrid-2-one (48d)**, was isolated as a cream solid: mp. 158-160°C; IR (KBr) 3382, 2953, 2930, 2866, 1729, 1643, 1524, 1468, 1202, 1044; ¹H NMR (d₆-DMSO) δ 8.26 (1H, s), 7.72 (1H, d), 7.39 (5H, m), 6.00 (1H, d), 5.14 (2H, s), 2.41 (2H, t), 1.52 (2H, m), 1.24 (2H, m), 0.87 (3H, t). Anal. Calcd for C₁₇H₂₀N₂O₃: C, 67.98; H, 6.71; N, 9.33. Found: C, 67.69; H, 6.68; N, 9.20. MS CI M⁺ = 300 (m) 28%.

20

(2S) Methyl 2-[3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl]propionate (**49a**). Sodium hydride (80% oil dispersion) (0.35g, 11.64mmole) was added to a stirred mixture of 3-(benzyloxycarbonylamino)pyrid-2-

25

- 175 -

one (48a) (2.58g, 10.58mmol) and tetrahydrofuran (100ml) at room temperature. The mixture was stirred for 10 mins. The resulting solution was added to a solution of 2(R) methyl-2((trifluoromethane) sulphonyloxy)propionate (2.5g, 10.58mmole; Feenstra et al., Tetrahedron Lett., 28, pp. 1215-18 (1987)) in tetrahydrofuran (5ml) at room temperature during 10 mins. The mixture was stirred at room temperature for 80 mins then poured into ethyl acetate. The mixture was washed twice with 1M HCl, twice with aqueous sodium bicarbonate then brine. It was dried (MgSO₄) and concentrated. The residue was purified by flash chromatography (30% ethyl acetate/hexane) to afford 2.945g (84%) of a colorless solid: mp. 96-7°; $[\alpha]_D^{20}$ - 71.36 (c 2.5, CHCl₃); IR (KBr) 3370, 1764, 1729, 1648, 1602, 1564, 1523, 1515, 1503, 1449, 1359, 1203, 1064; ¹H NMR(CDCl₃) δ 8.04 (1H, d, J=7.2), 7.86 (1H, s), 7.36 (5H, m), 6.98 (1H, dd, J=7.1, J=1.7), 6.30 (1H, t, J=7.2), 5.46 (1H, q, J=7.4), 5.20 (2H, s), 3.74 (3H, s), 1.66 (3H, d, J=7.4). Anal. Calcd for C₁₇H₁₈N₂O₅: C, 61.81; H, 5.49; N, 8.48. Found: C, 61.49; H, 5.51; N, 8.41. MS(FAB, m/z) 331 (M⁺ + 1), 299, 223, 196, 163, 91.

Methyl [6-benzyl-3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl]-acetate (49b). Sodium hydride (80% oil dispersion) (0.65g, 26.2mmole) was added to a stirred mixture of 6-benzyl-3(benzyloxycarbonylamino)pyrid-2-one (48b) (7.3g, 2.18mmol) and tetrahydrofuran (150ml) at room temperature. The mixture was stirred for 10mins, treated with methyl bromoacetate (2.5ml, 26.2mmol) and kept for 3h. The resulting mixture was poured onto a mixture of ice and 1M HCl. The resulting solid was filtered off then dissolved in dichloromethane. The resulting solution was dried

- 176 -

(MgSO₄), decolourized with charcoal and concentrated. The residue was purified by chromatography (2-5% ethyl acetate/dichloromethane) to afford 7.2g (81%) of colorless crystals: mp. 117-9°; IR (KBr) 3375, 1753, 1730, 1651, 1605, 1513, 1384, 1223, 1185, 1071; ¹H NMR (CDCl₃) δ 8.02 (1H, d, J=7.5), 7.78 (1H, s), 7.31 (8H, m), 7.10 (2H, m), 6.15 (1H, d, J=7.5), 5.20 (2H, s), 4.70 (2H, s), 3.88 (2H, s), 3.66 (3H, s).

The following compounds were prepared in a similar manner:

Methyl [3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-6-phenethyl-1-pyridyl]-acetate (49c). 97% yield: m.p. 102-4°C. IR (KBr) 3245, 3232, 1741, 1725, 1648, 1600, 1526, 1216; ¹H NMR (d₆-DMSO) δ 8.45 (1H, s), 7.76 (1H, d, J = 7.6), 7.35 (10H, m), 6.15 (1H, d, J = 7.6), 5.15 (2H, s), 4.85 (2H, s), 3.68 (3H, s), 2.86 (4H, s).

Methyl [3-benzyloxycarbonylamino-6-butyl-1,2-dihydro-2-oxo-1-pyridyl]-acetate (49d). 90% yield: mp. 111-112°C; IR (KBr) 3393, 1738, 1731, 1645, 1598, 1517, 1225, 1208; ¹H NMR (d₆-DMSO) δ 8.39 (1H, s), 7.78 (1H, d, J = 7.7), 7.35 (5H, m), 6.17 (1H, d, J = 7.7), 5.15 (2H, s), 4.80 (2H, s), 3.67 (3H, s), 1.38 (6H, m), 0.89 (3H, t).

Methyl [3-benzyloxycarbonylamino-1,2-dihydro-6-methyl-2-oxo-1-pyridyl]-acetate (49e). 84% yield as a colorless solid: mp. 115-6°C; IR (KBr) 3246, 1740, 1725, 1649, 1598, 1573, 1535, 1417, 1365, 1259, 1219, 1193, 1090, 1068, 1006; ¹H NMR (d₆-DMSO) δ 8.40 (1H, s), 7.75 (1H, d, J = 7.6), 7.38 (5H, m), 6.20 (1H, d, J = 7.6), 5.15 (2H, s), 4.85 (2H, s), 3.68 (3H, s), 2.26 (3H, s).

- 177 -

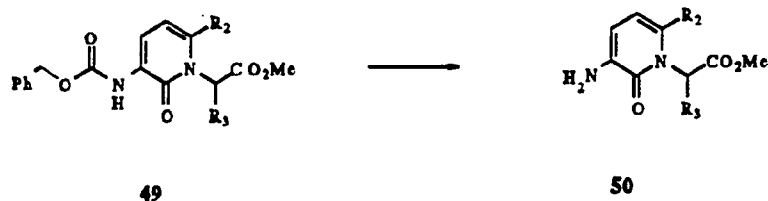
Methyl [3-benzyloxycarbonylamino-1,2-dihydro-6-phenyl-1-pyridyl]-acetate (49f). 67% yield as a colorless oil: IR (KBr) 3266, 1739, 1727, 1646, 1606, 1566, 1517, 1490, 1365, 1213, 1163, 1075; ¹H NMR (CDCl₃) δ 8.15 (1H, d), 7.85 (1H, s), 7.39 (10H, m), 6.22 (1H, d), 5.22 (2H, s), 4.57 (2H, s), 3.74 (3H, s).

Methyl [3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl]-acetate (49g). 80% yield as a colorless crystalline solid: m.p. 110-111°C. IR (KBr) 3385, 1745, 1726, 1650, 1601, 1512, 1502, 1378, 1369, 1358, 1215, 1195, 1162, 1067; ¹H NMR (CDCl₃) δ 8.06 (1H, d), 7.84 (1H, s), 7.36 (5H, m), 6.88 (1H, dd), 6.27 (1H, t), 5.20 (2H, s), 4.68 (2H, s), 3.78 (3H, s). Anal. Calcd for C₁₆H₁₆N₂O₅: C, 60.75; H, 5.10; N, 8.85. Found: C, 60.65; H, 5.15; N, 8.85. MS FAB (+)M⁺ = 317 (M + 1).

2(S) Methyl 2-methyl-[6-benzyl-(3-benzyloxycarbonylamino)-1,2-dihydro-2-oxo-1-pyridyl]-acetate (49h), was prepared by the method used in the preparation of compound 49a to afford (58%) an oil; [α]_D²⁵ -25.0° (c 1, CH₂Cl₂); IR (KBr) 3381, 1736, 1650, 1604, 1513, 1218, 1190, 1068; ¹H NMR (CDCl₃) δ 7.97 (1H, d), 7.78 (1H, s), 7.4-7.14 (10H, m), 6.17 (1H, d), 5.19 (2H, s), 4.64 (1H, q), 3.98 (2H, s), 3.62 (3H, s), 1.31 (3H, d).

Methyl [6-benzyl-1,2-dihydro-2-oxo-3-(2-phenylethoxy)-carbonylamino-1-pyridyl]acetate (49i), was isolated (88%) as a colorless solid: mp. 130-133°C; IR (KBr) 3363, 1746, 1732, 1651, 1604, 1515, 1368, 1231, 1212, 1185; ¹H NMR (CDCl₃) δ 8.00 (1H, d, J = 7.0), 7.68 (1H, s), 7.36-7.10 (10H, m), 6.15 (1H, d, J = 7.6), 4.7 (2H, s), 4.38 (2H, t, J = 7.0), 3.88 (2H, s), 3.67 (3H, s), 2.98 (2H, t, J = 7).

- 178 -



2(*S*) Methyl 2[3-amino-1,2-dihydro-2-oxo-1-pyridyl]propionate (50a). A mixture of 2(*S*) methyl-2[3-benzoyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl]propionate (49a) (2.75g, 8.33mmol), methanol (100ml), and 10% palladium on carbon (300mg) was stirred under an atmosphere of hydrogen for 30min. The mixture was filtered and concentrated to afford 1.63g (100%) of a colorless solid: ^1H NMR (d_6 -DMSO) δ 8.35 (1H, brs), 7.46 (1H, d), 7.22 (1H, d), 6.29 (1H, t), 5.22 (1H, q), 3.63 (3H, s), 1.55 (3H, d).

The following compounds were prepared in a similar manner:

15 Methyl [3-amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl]acetate (50b). 100% yield as a grey solid: mp. 134-6°C; IR (KBr) 3418, 3312, 1723, 1658, 1596, 1548, 1435, 1290, 1245, 1011; ^1H NMR (d_6 -DMSO) δ 7.25 (5H, m), 6.45 (1H, d, $J = 7.4$), 5.92 (1H, d, $J = 7.4$), 5.00 (2H, s), 4.63 (2H, s), 3.88 (2H, s), 3.51 (3H, s).

25 Methyl [3-amino-1,2-dihydro-2-oxo-6-phenethyl-1-pyridyl]acetate (50c). 99% yield as a viscous oil: IR (KBr) 3456, 341, 2953, 1745, 1649, 1600, 1548, 1219; ^1H NMR (CDCl_3) δ 7.25 (5H, m), 6.51 (1H, d, $J = 7.4$), 5.92 (1H, d, $J = 7.4$), 4.79 (2H, s), 3.77 (3H, s), 2.80 (4H, m).

- 179 -

Methyl[3-amino-6-butyl-1,2-dihydro-2-oxo-1-pyridyl]acetate (50d). 97% as a brown solid: mp. 75-7°C; IR (KBr) 3437, 3342, 2955, 1745, 1655, 1609, 1550, 1432, 1301, 1222, 1200; ¹H NMR (CDCl₃) δ 6.53 (1H, d, *J* = 6.8), 5.93 (1H, d, *J* = 6.8), 4.81 (2H, s), 3.77 (3H, s), 2.44 (2H, t), 1.45 (4H, m), 0.93 (3H, t).

Methyl[3-amino-1,2-dihydro-6-methyl-2-oxo-1-pyridyl]acetate (50e), was isolated (100%) as a colorless crystalline solid: mp. 87-9°C; IR (KBr) 3442, 3326, 1735, 1647, 1600, 1549, 1434, 1407, 1383, 1366, 1225, 1209; ¹H NMR (d₆-DMSO) δ 6.40 (1H, d, *J* = 7.3), 5.93 (1H, d, *J* = 7.3), 4.86 (2H, s), 4.79 (2H, s), 3.67 (3H, s), 2.15 (3H, s).

Methyl[3-amino-1,2-dihydro-2-oxo-6-phenyl-1-pyridyl]acetate (50f), was isolated (86%) as a grey solid: mp. 207-9°C; IR (KBr) 3473, 3345, 1750, 1644, 1600, 1536, 1443, 1366, 1309, 1212, 1184, 1156; ¹H NMR (d₆-DMSO) δ 7.30 (5H, m), 6.54 (1H, d), 6.03 (1H, d), 5.25 (2H, s), 4.49 (2H, s), 3.61 (3H, s).

Methyl[3-amino-1,2-dihydro-2-oxo-1-pyridyl]acetate (50g), was obtained as a colorless oil and used immediately in the next step.

2(S) Methyl 2-methyl-[3-amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl]acetate (50h), was isolated (69%) as a colorless oil: IR (film) 3354, 1743, 1646, 1600, 1548, 1494, 1455, 1309, 1268, 1227, 1113; ¹H NMR (C₆D₆) δ 7.29-6.76 (5H, m), 5.86 (1H, d, *J* = 7.2), 5.51 (1H, d, *J* = 7.2), 4.43 (1H, q, *J* = 6.7), 3.69 (2H, s), 3.41 (2H, s), 3.36 (3H, s), 1.43 (3H, d, *J* = 6.7).

- 180 -



	R_1	R_2	R_3
	(a) $\text{Ph}(\text{CH}_2)_2\text{CO}$	H	(S) Me
	(b) $\text{Ph}(\text{CH}_2)_2\text{CO}$	CH_2Ph	H
5	(c) $\text{Ph}(\text{CH}_2)_2\text{CO}$	$(\text{CH}_2)_2\text{Ph}$	H
	(d) $\text{Ph}(\text{CH}_2)_2\text{CO}$	nBu	H
	(e) $\text{Ph}(\text{CH}_2)_2\text{CO}$	Me	H
	(f) $\text{Ph}(\text{CH}_2)_2\text{CO}$	Ph	H
	(g) $\text{Ph}(\text{CH}_2)_2\text{CO}$	H	H
10	(h) $\text{Ph}(\text{CH}_2)_2\text{CO}$	CH_2Ph	(S) -Me or (R, S) -Me
	(i) AcTyr	CH_2Ph	H
	(j) $\text{Ph}(\text{CH}_2)_2\text{SO}_2$	CH_2Ph	H
	(k) $\text{Ph}(\text{CH}_2)_2\text{OCO}$	CH_2Ph	H
15	(l) $\text{Ph}(\text{CH}_2)_3\text{CO}$	CH_2Ph	H

2(S) Methyl 2-[1,2-dihydro-2-oxo-3-(3-phenylpropionyl) amino-1-pyridyl]- propionate (51a). 3-Phenylpropionyl chloride (1.5g, 9mmol) was added dropwise to a stirred mixture of 2S methyl-2-[3-amino-1,2-dihydro-2-oxo-1-pyridyl]propionate (50a) (1.63g, 8.33mmol), dioxane (60ml), water (15ml) and sodium bicarbonate (1.54g, 16.7mmol). The mixture was kept for 1h then extracted with ethyl acetate. The extracts were washed with aqueous sodium bicarbonate, dried (MgSO_4) and concentrated. The resulting red oil was purified by flash chromatography to afford 2.54g (93%) of an oil:

- 181 -

[α]_D²⁰ -68°C (1, CH₂Cl₂); IR (CH₂Cl₂) 3369, 1747, 1690, 1650, 1602, 1512, 1267, 1260, 1217; ¹H NMR (CDCl₃) δ 8.41 (1H, dd), 8.36 (1H, s), 7.24 (5H, m), 7.02 (1H, dd), 6.32 (1H, t), 5.44 (1H, q), 3.75 (3H, s), 3.03 (2H, t), 2.70 (2H, t), 1.66 (3H, d). FAB M⁺ = 329 (M + 1), 197, 165, 131, 110, 91.

The following compounds were prepared in a similar manner:

Methyl [6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51b), was isolated (93%) as crystals: mp. 95-7°C; IR (KBr) 3265, 1747, 1686, 1642, 1590, 1563, 1511, 1454, 1401, 1220, 1183, 1133; ¹H NMR (CDCl₃) δ 8.39 (1H, d, *J* = 7.7), 8.27 (1H, s), 7.21 (10H, m), 6.17 (1H, d, *J* = 7.7), 4.70 (2H, s), 3.89 (2H, s), 3.67 (3H, s), 3.02 (2H, m), 2.70 (2H, m).

Methyl [1,2-dihydro-2-oxo-6-phenethyl-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51c), was isolated (81%) as colorless crystals: mp. 105-8°C; IR (KBr) 3378, 1746, 1680, 1646, 1597, 1517, 1221; ¹H NMR (CDCl₃) δ 8.34 (1H, d, *J* = 7.7), 8.25 (1H, s), 7.23 (10H, m), 6.11 (1H, d, *J* = 7.7), 4.77 (2H, s), 3.78 (3H, s), 2.88 (8H, m).

Methyl [6-butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51d), was isolated (88%) as colorless crystals: mp. 84-5°C; IR (KBr) 3345, 2958, 2930, 1756, 1693, 1650, 1602, 1510, 1227, 1180, 1137; ¹H NMR (CDCl₃) δ 8.34 (1H, d, *J* = 7.7), 8.22 (1H, s), 7.26 (5H, m), 6.12 (1H, d, *J* = 7.7), 4.80 (2H, s), 3.79 (3H, s), 3.03 (2H, t), 2.68 (2H, t), 2.50 (2H, t), 1.46 (4H, m), 0.95 (3H, t).

- 182 -

Methyl [1,2-dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51e), was isolated (100%) as a pale yellow oil: IR (film) 3264, 1745, 1691, 1644, 1587, 1566, 1518, 1495, 1400, 1215, 1183, 1136; ^1H NMR (CDCl_3) δ 8.33 (1H, d, $J = 7.6$), 7.26 (5H, m), 6.13 (1H, d, $J = 7.6$), 4.83 (2H, s), 3.79 (3H, s), 3.03 (2H, m), 2.69 (2H, m), 2.28 (3H, s).

Methyl [1,2-dihydro-2-oxo-6-phenyl-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51f), was isolated (99%) as a pale yellow oil: IR (film) 3365, 3299, 1751, 1689, 1643, 1600, 1563, 1519, 1493, 1419, 1370, 1224; ^1H NMR (CDCl_3) δ 8.46 (1H, d, $J = 7.7$), 8.32 (1H, s), 7.32 (10H, m), 6.24 (2H, d, $J = 7.7$), 4.57 (2H, s), 3.73 (3H, s), 3.06 (2H, m), 2.72 (2H, m).

Methyl [1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51g), was isolated (81%) as an oil: IR (film) 3330, 1753, 1689, 1650, 1600, 1560, 1517, 1374, 1225, 1208; ^1H NMR (CDCl_3) δ 8.43 (1H, dd, $J = 7.4, 1.7$), 8.33 (1H, s), 7.28 (5H, m), 6.92 (1H, dd, $J = 6.9, 1.7$), 6.29 (1H, t), 4.67 (2H, s), 3.79 (3H, s), 3.04 (2H, m), 2.70 (2H, m). MS FAB (+) $M + = 315$ ($M + 1$).

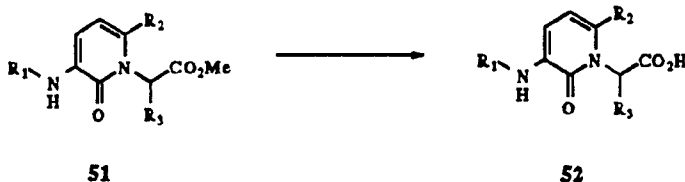
2(S) Methyl 2-methyl-[6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-acetate (51h), was isolated (93%) as a colorless oil; $[\alpha]_D^{30} -19^\circ$ (c 1, CH_2Cl_2); IR (film) 3354, 3313, 3028, 2950, 1745, 1687, 1645, 1600, 1567, 1514, 1454, 1225; ^1H NMR (CDCl_3) δ 8.35 (1H, d, $J = 7.5$), 8.26 (1H, s), 7.27 (10H, m), 6.20 (1H, d, $J = 7.5$), 4.65 (1H, q, $J = 6.8$), 3.99 (2H, s), 3.71 (3H, s), 3.03 (2H, m), 2.68 (2H, m), 1.31 (3H, d, $J = 6.8$).

- 183 -

Methyl [3-(N-acetyl-O-benzyl-L-tyrosine)amino-6-benzyl-1,2-dihydro-2-oxo-pyridyl]acetate (51i). A stirred mixture of methyl [3-amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl]acetate (100mg, 0.367mmol), Boc-Tyr(Bn)-OH (136mg, 0.367mmol), dimethylformamide (1ml), diisopropylethylamine (0.25ml, 1.468mmol) and 2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (118mg, 0.367mmol) was kept overnight at room temperature. The mixture was diluted with ethyl acetate, washed twice with 1M hydrochloric acid, twice with aqueous sodium bicarbonate, once with brine, then dried (MgSO_4) and concentrated. The residue was purified by flash chromatography (10% ethyl acetate/dichloromethane) to afford a 162mg (70%) of a colorless oil. The oil (160mg, 0.255mmol) was dissolved in dichloromethane (1ml) and treated with trifluoroacetic acid (1ml) at 0°C. The resulting solution was allowed to reach room temperature during 40min then evaporated to dryness at 30°C. The residue was dissolved in dichloromethane then evaporated to dryness again. This procedure was repeated three times. The residue was dissolved in pyridine (0.5ml) and treated with acetic anhydride (0.03ml, 0.3mmol) at 0°C. The resulting mixture was allowed to reach room temperature and kept for 3.5h. It was diluted with ethyl acetate, washed twice with 1M hydrochloric acid, twice with aqueous sodium bicarbonate, dried (MgSO_4) and concentrated to afford 128mg (86%) of a colorless oil: IR (film) 3290, 1751, 1649, 1602, 1568, 1513, 1455, 1438, 1375, 1224, 1179; ^1H NMR (CDCl_3) δ 8.78 (1H, s), 8.33 (1H, d, J = 7.6), 7.33 (8H, m), 7.11 (4H, m), 6.86 (2H, d, J = 8.5), 6.47 (1H, d, J = 7.6), 6.12 (1H, d, J = 7.6), 4.99 (2H, s), 4.85 (1H, m), 4.69 (2H, s), 3.87 (2H, s), 3.62 (3H, s), 3.08 (2H, m), 1.96 (3H, s).

- 184 -

- Methyl [6-benzyl-1,2-dihydro-2-oxo-3-(2-phenylethanesulphonyl)amino-1-pyridyl]-acetate (51j). 2-Phenylethanesulphonyl chloride (Zhong et al., J. Am. Chem. Soc., 113, pp. 2259-63 (1991)) was added to a stirred mixture of methyl [3-amino-6-benzyl-2-oxo-1,2-dihydro-1-pyridyl]-acetate (49b) (1.0g, 3.67mmol), dichloromethane (15ml) and triethylamine (1.0ml, 7.34mmol). The mixture was kept overnight then poured into ethyl acetate. The resulting mixture was washed twice with aqueous sodium bicarbonate, three times with 1M hydrochloric acid, then brine. It was dried (MgSO₄) and concentrated. The resulting pale brown solid was purified by flash chromatography (10% ethyl acetate/dichloromethane) to afford 1.25g (77%) of a pale yellow solid: m.p. 92-4°C; IR (KBr) 3181, 1737, 1646, 1595, 1565, 1454, 1241, 1220, 1150; ¹H NMR (CDCl₃) δ 7.53 (1H, d, J = 7.5), 7.29 (10H, m), 6.10 (1H, d, J = 7.5), 4.75 (2H, s), 3.89 (2H, s), 3.67 (3H, s), 3.34 (2H, m), 3.14 (2H, m).
- Methyl [6-benzyl-1,2-dihydro-2-oxo-3-(4-phenylbutyryl)amino-1-pyridyl]-acetate (51l), was isolated (74%) as colorless crystals: mp. 93-95°C; IR (KBr) 3285, 1747, 1683, 1642, 1591, 1563, 1512, 1455, 1220, 1181; ¹H NMR (CDCl₃) δ 8.39 (1H, d, J = 7.6), 8.24 (1H, s), 7.2 (10H, m), 6.18 (1H, d, J = 7.6), 4.7 (2H, s), 3.90 (2H, s), 3.67 (3H, s), 2.69 (2H, t), 2.40 (2H, t), 2.04 (2H, m).



- 185 -

2(S) 2-[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino]-
1-pyridyl]propionic acid (52a). 1M Sodium hydroxide
(15ml, 15mmol) was added to a stirred solution of 2(S)
methyl 2-[1,2-dihydro-2-oxo-3(3-phenylpropionyl)amino-
5 1-pyridyl]propionate (51a) (2.39g, 7.3mmol) in methanol
(30ml) at 0°C. The mixture was kept at this
temperature for 2h, acidified with 1M hydrochloric acid
(15.1ml) and extracted with ethyl acetate. The
extracts were washed with brine, dried (MgSO₄) and
10 concentrated to afford 1.98g (87%) of a colorless
solid: $[\alpha]_D^{20}$ -75° (1, CH₂Cl₂); IR (KBr) 3301, 1724,
1693, 1637, 1563, 1523, 1453, 1233, 1216, 765; ¹H NMR
(CDCl₃) δ 8.47 (2H, m), 7.20 (5H, m), 7.03 (1H, d), 6.36
(1H, t), 5.35 (1H, q), 3.01 (2H, m), 2.70 (2H, m), 1.69
15 (3H, m).

The following compounds were prepared in a similar
manner:

[6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-
1-pyridyl]acetic acid (52b), was isolated (100%) as a
20 pale amber oil: IR (film) 3291, 1738, 1686, 1644,
1591, 1554, 1519, 1496, 1454, 1403, 1215, 1182; ¹H NMR
(CDCl₃) δ 8.44 (1H, d, *J* = 7.8), 8.4 (1H, s), 7.21 (10H,
m), 6.19 (1H, d, *J* = 7.8), 4.71 (2H, s), 3.90 (2H, s),
2.99 (2H, m), 2.71 (2H, m).

25 [1,2-Dihydro-2-oxo-6-phenethyl-3-(3-phenylpropionyl)
amino-1-pyridyl]acetic acid (52c), was isolated (94%)
as a beige solid: mp. 214-6°C; IR (KBr) 3289, 1740,
1680, 1640; ¹H NMR (d₆-DMSO) δ 9.24 (1H, s), 8.14 (1H,
d, *J* = 7.7), 7.22 (10H, m), 6.11 (1H, d, *J* = 7.8), 4.78
30 (2H, s), 2.81 (8H, m).

- 186 -

[6-Butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]acetic acid (52d), was isolated (99%) as a pale brown solid: mp. 132-4°C; IR (KBr) 3286, 1739, 1676, 1641, 1584, 1555, 1535, 1455, 1414, 1249, 1227, 1204; ¹H NMR (CDCl₃) δ 8.42 (1H, d, J = 7.8), 8.37 (1H, s), 7.24 (5H, m), 6.19 (1H, d, J = 7.8), 4.82 (2H, s), 3.55 (1H, s), 3.00 (2H, t), 2.67 (2H, t), 2.53 (2H, t), 1.41 (4H, m), 0.94 (3H, t).

[1,2-Dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]acetic acid (52e), was isolated as a solid (100%): mp. 159-61°C; IR (KBr) 3335, 1731, 1686, 1642, 1536, 1516, 1430, 1420, 1401, 1222, 1195; ¹H NMR (d₆-DMSO) δ 9.21 (1H, s), 8.13 (1H, d, J = 7.6), 7.20 (5H, m), 6.15 (1H, d, J = 7.6), 4.77 (2H, s), 2.87 (2H, m), 2.70 (2H, m), 2.25 (3H, s).

[1,2-Dihydro-2-oxo-6-phenyl-3-(3-phenylpropionyl)amino-1-pyridyl]acetic acid (52f), was isolated (100%) as a pale yellow foam: IR (KBr) 3271, 1747, 1683, 1634, 1580, 1536, 1490, 1406, 1392, 1365, 1235, 1219; ¹H NMR (CDCl₃) δ 8.52 (1H, d, J = 7.7), 7.31 (10H, m), 6.48 (2H, s), 6.30 (1H, d, J 7.7), 4.60 (2H, s), 3.03 (2H, m), 2.71 (2H, m).

[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]acetic acid (52g), was isolated (94%) as a colorless solid: mp. 195-7°C; IR (KBr) 3324, 1724, 1693, 1644, 1569, 1555, 1512, 1427, 1370, 1240; ¹H NMR (d₆-DMSO) δ 9.31 (1H, s), 8.23 (1H, d, J = 6.8), 7.36 (1H, dd, J = 6.8, 1.71), 7.25 (5H, m), 6.25 (1H, t), 4.66 (2H, s), 2.84 (4H, m).

2(R,S) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-propionic acid (52h),

- 187 -

was prepared by hydrolysis of compound 51h in aqueous tetrahydrofuran during 5h at 40°C to afford (95%) as a yellow oil: IR (film) 3330, 1734, 1686, 1643, 1600, 1587, 1553, 1524, 1498, 1208; ¹H NMR (d₆-DMSO) δ 9.29 (1H, s), 8.18 (1H, d, J = 7.6), 7.21 (10H, m), 6.22 (1H, d, J = 7.6), 4.82 (1H, q, J = 6.6), 4.08 (2H, m), 2.76 (4H, m), 1.05 (3H, d, J = 6.6).

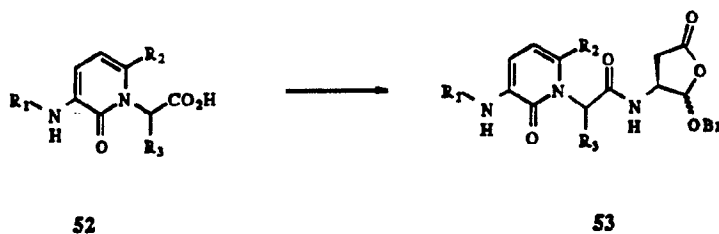
[3-(Acetyl-Tyr(Bn))amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl]acetic acid (52i), was isolated (93%) as a foam: IR (KBr) 3302, 1731, 1646, 1603, 1562, 1512, 1454, 1428, 1379, 1231, 1178; ¹H NMR (CDCl₃) δ 9.48 (1H, s), 8.36 (1H, d, J = 7.6), 7.30 (8H, m), 7.10 (2H, m), 6.85 (2H, d, J = 8.3), 6.91 (2H, d, J = 8.3), 6.71 (1H, d, J 7.6), 4.95 (1H, m), 4.90 (2H, s), 4.68 (2H, s), 3.92 (2H, s), 3.17-2.83 (2H, m), 1.92 (3H, s).

[6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethanesulphonyl)amino-1-pyridyl]acetic acid (52j), was isolated (100%) as a colorless solid: mp. 165-7°C; IR (KBr) 3174, 1760, 1646, 1593, 1567, 1497, 1453, 1424, 1326, 1225, 1140, 1127; ¹H NMR (d₆-DMSO) δ 13.09 (1H, s), 9.08 (1H, s), 7.30 (11H, m), 6.02 (1H, d), 4.68 (2H, s), 4.99 (2H, s), 3.29 (2H, m), 3.03 (2H, m).

[6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethoxy)carbonylamino-1-pyridyl]acetic acid (52k), was prepared (70%) by hydrolysis of compound 49i during 1h at 60°C: IR (CH₂Cl₂) 1797, 1689, 1649, 1601, 1512, 734; ¹H NMR (CDCl₃) δ 8.39 (1H, s), 8.03 (1H, d), 7.81 (1H, s), 7.33-7.07 (10H, m), 6.13 (1H, d, J = 7.8), 4.72 (2H, s), 4.33 (2H, t, J = 7.0), 3.86 (2H, s), 2.93 (2H, t, J = 7.0).

- 188 -

[6-Benzyl-1,2-dihydro-2-oxo-3-(4-phenylbutyryl)amino-1-pyridyl]acetic acid (521), was isolated (100%) as a white foam: m.p. 159-161°C; IR (KBr) 3373-3310, 1787, 1726, 1691, 1649, 1599, 1567, 1517, 1367, 1215; ¹H NMR (CDCl₃) δ 8.43 (1H, d, *J* = 7.7), 8.25 (1H, s), 7.37-7.09 (10H, m), 6.21 (1H, d, *J* = 7.7), 4.73 (2H, s), 4.15 (3H, s), 3.91 (2H, s), 2.67 (2H, t), 2.39 (2H, t), 2.02 (2H, m).



2(*S*), N-3(*S*) 2-[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)propionamide (53a). Tri-*n*-butyltin hydride (1.7ml, 6.3mmol) was added dropwise to a stirred mixture of 2(*S*)-2-[1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]propionic acid (52a) (1.1g, 3.49mmol), 3(*S*), 2(*R,S*) 3-allyloxycarbonylamino-2-benzyloxy-5-oxotetrahydrofuran (1.02g, 3.49mmol; Chapman, Biorg. Med. Chem. Lett., 2, pp. 613-18 (1992)), bis(triphenylphosphine)palladium (II) chloride (55mg), dichloromethane (35ml) and dimethylformamide (1ml). The resulting mixture was stirred for 5 min. then 1-hydroxybenzotriazole (946mg, 7mmol) was added. The mixture was cooled to 0°C before the addition of 1-(3-dimethylaminopropyl)-2-ethylcarbodiimide hydrochloride (740mg, 3.84mmol). The mixture was kept overnight at room temperature then poured into ethyl acetate. The mixture was washed twice with 1M hydrochloric acid, twice with aqueous sodium bicarbonate, then brine. The mixture was dried (MgSO₄)

- 189 -

and concentrated. The residue was triturated with pentane. The remaining solid was purified by flash chromatography (40-60% ethyl acetate/hexane) to afford 1.28g (73%) of colorless solid: IR (KBr) 1796, 1692, 1647, 1595, 1557, 1512, 1119; ¹H NMR (d₆-DMSO) δ 9.28, 9.26 (1H, 2 x s), 8.77, 8.69 (1H, 2 x d), 8.24, 8.20 (1H, 2 x dd), 7.20 (11H, m), 6.31, 6.26 (1H, 2 x t), 5.65 (0.5H, d), 5.46 (0.5H, d), 5.41, 5.28 (1H, 2 x q), 4.7 (2.5H, m), 4.24 (0.5H, t), 3.24 (2H, m), 2.80 (4H, m), 1.51, 1.46 (3H, 2 x d).

The following compounds were prepared in a similar manner:

N(3(S)) 2[6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53b), was obtained (86%) as a foam: IR (KBr) 3345, 3297, 1807, 1791, 1688, 1679, 1650, 1602, 1554, 1525, 1497, 1453, 1372, 1257, 1119; ¹H NMR (d₆-DMSO) δ 9.25 (0.5H, s), 9.23 (0.5H, s), 8.75 (0.5H, d, J = 6.5), 8.67 (0.5H, d, J = 7.4), 8.18 (1H, 2d), 7.21 (15H, m), 6.07 (1H, 2d), 5.65 (0.5H, d, J = 5.0), 5.38 (0.5H, s), 4.83-4.45 (4.5H, m), 4.19 (0.5H, m), 3.94, 3.83 (2H, m), 3.10-2.31 (6H, m).

N(3(S)) 2[1,2-Dihydro-2-oxo-6-phenethyl-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-4-yl)acetamide (53c), was obtained (74%) as a mixture of anomers: ¹H NMR (d₆-DMSO) δ 9.71 (1H, d), 9.41 (0.5H, d), 9.25 (0.5H, d), 8.64 (1H, d, J = 7.7), 7.75 (15H, m), 6.61 (1H, 2d), 6.11 (0.5H, d), 5.93 (0.5H, s), 5.17 (5H, m), 4.77 (0.5H, m), 3.68-2.94 (2H, m), 3.32 (8H, m).

- 190 -

- N(3(S)) 2[6-Butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53d)**, was obtained (74%) as a mixture of anomers: IR (KBr) 3300, 1791, 1689, 1645, 1597, 1566, 1546, 1514, 1454, 1417, 1378; ¹H NMR (CDCl₃) δ 8.38 (1H, d, *J* = 7.7), 8.13 (1H, s), 7.30 (10H, m), 6.18 (1H, t), 5.47 (0.5H, d, *J* = 5.2), 5.43 (0.5H, s), 4.75 (4.5H, m), 4.38 (0.5H, m), 3.08-2.35 (8H, m), 1.43 (4H, m), 0.95 (3H, t).
- N(3(S)) 2[1,2-Dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53e)**, was obtained (67%) as a mixture of anomers: IR (KBr) 3282, 1774, 1667, 1651, 1596, 1561, 1556, 1498, 1265, 1254, 1236, 1199, 1143; ¹H NMR (d₆-DMSO) δ 9.17 and 9.15 (1H, 2 x s), 8.89 (0.5H, d, *J* = 6.5), 8.73 (0.5H, d, *J* = 7.4), 7.25 (10H, m), 6.13 (1H, t), 5.64 (0.5H, d, *J* = 5.0), 5.45 (0.5H, s), 4.89-4.61 (4.5H, m), 4.26 (0.5H, m), 3.17-2.36 (6H, m), 2.23 and 2.15 (3H, 2s).
- N(3(S)) 2-[1,2-Dihydro-2-oxo-6-phenyl-3(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53f)**, was obtained (73%) as a mixture of anomers: IR (KBr) 3296, 1792, 1691, 1643, 1595, 1561, 1514, 1489, 1453, 1420, 1373, 1230, 1118; ¹H NMR (d₆-DMSO) δ 9.40, 9.36 (1H, 2s), 8.70 (0.5H, d, *J* = 7.6), 8.52 (0.5H, d, *J* = 7.5), 8.29 (1H, dd), 7.25 (15H, m), 6.20 (1H, d, *J* = 7.6), 5.61 (0.5H, d, *J* = 5.0), 5.28 (0.5H, s), 4.78-4.20 (5H, m), 3.12-2.24 (6H, m).
- N(3(S)) 2-[1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53g)**, was obtained (70%) as a mixture of

- 191 -

anomers: IR (KBr) 3336, 3290, 1791, 1691, 1646, 1595, 1582, 1556, 1518, 1454, 1376, 1351, 1150, 1122; ¹H NMR (d₆-DMSO) δ 9.26 (1H, 2s), 8.86 (0.5H, d, J = 6.4), 8.67 (0.5H, d, J = 7.5), 8.23 (1H, m), 7.40-7.13 (11H, m), 6.24 (1H, 2t, J = 7.2), 5.61 (0.5H, d, J = 5.0), 5.44 (0.5H, s), 4.83-4.59 (2.5H, m), 4.25 (0.5H, m), 3.15-2.34 (2H, m), 2.91-2.70 (4H, m). Anal. Calc. for C₂₇H₂₇N₃O₆ H₂O: C, 63.90; H, 5.76; N, 8.28. Found: C 63.70; H, 5.68; N, 8.22. MS FAB M⁺ = 490 (M + 1).

10 2(R, S), N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N(2-benzyloxy-5-oxotetrahydrofuran-3-yl)propionamide (53h), was obtained (89%) as a mixture of diastereomers. Data is given for a single diastereomer: IR (film) 3356, 1788, 1677, 1645, 1602, 1517, 1455, 1377, 1203, 1167, 1120; ¹H NMR (CDCl₃) δ 8.34 (1H, d, J = 7.6), 8.19 (1H, s), 7.38-7.13 (10H, m), 6.26 (1H, d, J = 7.6), 5.58 (1H, t), 5.31, 5.24 (1H, 2 x s), 4.62 (2H, 2q), 4.60 (1H, m), 4.27 (1H, m), 2.98, 2.68 (4H, 2m), 3.0-2.0 (2H, m), 1.42 (3H, d).

25 N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(N-acetyl-O-benzyltyrosinyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53i), was obtained (76%) as a mixture of anomers: IR (KBr) 1794, 1698, 1651, 1612, 1514, 1454, 1374, 1247, 1177, 1126; ¹H NMR (d₆-DMSO) δ 9.34, 9.31 (2 x 0.5H, 2s), 8.71 (1H, 2d), 8.38 (1H, m), 8.17 (1H, d), 7.48-6.88 (19H, m), 6.08 (1H, 2d), 5.65 (0.5H, d, J = 5.0), 5.40 (0.5H, s), 5.04 (2H, s), 4.68 (5.5H, m), 4.15 (0.5H, m), 3.95, 3.84 (2H, s + abq), 3.20-2.40 (4H, m), 1.78 (3H, s).

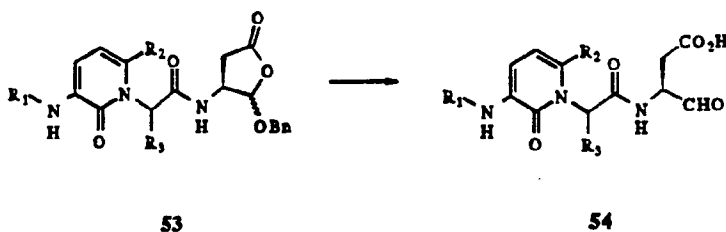
- 192 -

N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethanesulphonyl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53j), was obtained (78%) as a mixture of anomers: IR (KBr) 3344, 1792, 1691, 1647, 1599, 1566, 1454, 1365, 1150, 1121, 973; ¹H NMR (d₆-DMSO) δ 9.02, 8.99 (1H, 2s), 8.80 (0.5H, d, *J* = 6.4), 8.70 (0.5H, d, *J* = 7.4), 7.26 (15H, m), 6.00 (1H, dd), 5.63 (0.5H, d, *J* = 5.0), 5.39 (0.5H, s), 4.68 (4.5H, m), 4.18 (0.5H, m), 3.90 (2H, m), 3.30-2.30 (6H, m).

N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethoxy)carbonylamino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53k), was obtained (78%) as a mixture of anomers: IR (KBr) 3386, 1794, 1726, 1650, 1603, 1518, 1366, 1214, 699; ¹H NMR (CDCl₃) δ 8.03 (1H, bd), 7.63, 7.61 (1H, 2 x s), 7.34-7.04 (15H, m), 6.21, 6.18 (1H, 2d), 5.44 (0.5H, d, *J* = 5.4), 5.37 (0.5H, s), 4.85, 4.83 (1H, 2d, *J* = 11.6, 11.5), 4.61-4.48, 4.32 (4H, 2m), 4.4 (2H, t), 4.08, 4.03 (2H, 2bs), 3.07-2.78 (3H, m), 2.47-2.30 (1H, m).

N(3(S)) 2-[6-Benzyl-1,2-dihydro-2-oxo-3-(4-phenylbutyryl)amino-1-pyridyl]-N-(2-benzyloxy-5-oxotetrahydrofuran-3-yl)acetamide (53l), was obtained (86%) as a colorless oil: IR (CH₂Cl₂) 1797, 1689, 1649, 1601, 1512, 734; ¹H NMR (CDCl₃) δ 8.42, 8.40 (1H, 2d, *J* = 7.6), 7.35-7.07 (15H, m), 6.21, 6.19 (1H, 2d, *J* = 7.6), 5.44 (0.5H, d), 5.37 (0.5H, s), 4.84, 4.81 (1H, 2d, *J* = 11.7, 11.4), 4.73-4.48, 4.34 (4H, 2m), 4.05 (2H, m), 3.05-2.63, 2.46-2.30 (6H, 2m), 2.01 (2H, m).

- 193 -



	R_1	R_2	R_3
	(a) $\text{Ph}(\text{CH}_2)_2\text{CO}$	H	(S) Me
	(b) $\text{Ph}(\text{CH}_2)_2\text{CO}$	CH_2Ph	H
	(c) $\text{Ph}(\text{CH}_2)_2\text{CO}$	$(\text{CH}_2)_2\text{Ph}$	H
5	(d) $\text{Ph}(\text{CH}_2)_2\text{CO}$	nBu	H
	(e) $\text{Ph}(\text{CH}_2)_2\text{CO}$	Me	H
	(f) $\text{Ph}(\text{CH}_2)_2\text{CO}$	Ph	H
	(g) $\text{Ph}(\text{CH}_2)_2\text{CO}$	H	H
	(h) $\text{Ph}(\text{CH}_2)_2\text{CO}$	CH_2Ph	(R, S) -Me
10	(i) AcTyr	CH_2Ph	H
	(j) $\text{Ph}(\text{CH}_2)_2\text{SO}_2$	CH_2Ph	H
	(k) $\text{Ph}(\text{CH}_2)_2\text{OCO}$	CH_2Ph	H
	(l) $\text{Ph}(\text{CH}_2)_3\text{CO}$	CH_2Ph	H

15 **3(S), N(2(S)) 3-(2-(1,2-Dihydro-2-oxo-3-(3-phenylpropionylamino-1-pyridyl)-propionylamino)-4-oxo-butanoic acid (54a; F).** A mixture of 2(S), N(3(S)) 2-[1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl]-N(2-benzyloxy-5-oxotetrahydro-furan-3-yl)propionamide **53a** (1.28g, 2.5mmol), methanol (140ml)

20 ethyl acetate (60ml) and 10% palladium on carbon (1.4g) was stirred under an atmosphere of hydrogen. After 2.5h more catalyst (300mg) was added and hydrogenation continued for 1h. The mixture was filtered through Celite™ and then refiltered through 0.2μM nylon filter

- 194 -

and concentrated. The residual oil triturated with a mixture of methanol and ether to afford 916mg (87%) of colorless crystals: mp. 198-200°C; $[\alpha]_D^{28}$ -120° (0.1, CH₃OH); IR (KBr) 3330, 1794, 1688, 1644, 1583, 1556, 1515, 1427; ¹H NMR (CD₃OD) δ 8.28 (1H, d), 7.35 (1H, d), 7.20 (5H, m), 6.36 (1H, t), 5.49 (1H, q), 4.59 (1H, t), 4.25 (1H, m), 2.98, 2.74 (2 x 2H, 2 x m), 2.59 (2H, m), 1.57 (3H, d). Anal. Calcd for C₂₁H₂₃N₃O₆ 0.75 H₂O: C, 59.08; H, 5.78; N, 9.84. Found: C 59.24; H, 5.96; N, 9.84. FAB M⁺ = 414 (M + 1), 297, 165, 91.

The following compounds were prepared in a similar manner:

3(S) 3-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid, (54b; M), was isolated (59%) as colorless crystals: mp. 115°C (decomp); IR (KBr) 3440, 3297, 1718, 1646, 1598, 1565, 1526, 1496, 1260; ¹H NMR (CD₃OD) 8.25 (1H, d, J=7.7), 7.25 (10H, m), 6.15 (1H, 2d, each J=7.7), 4.73 (2H, 2q), 4.59 (1H, m), 4.30 (1H, m), 3.95 (2H, s), 2.98 (2H, m), 2.75 (2H, m), 2.8-2.42 (2H, m). Anal. Calcd for C₂₇H₂₇N₃O₆ 0.7 H₂O: C, 64.58; H, 5.70; N, 8.37. Found: C, 64.51; H, 5.63; N, 8.38. MS FAB+ M+ = 490 (M + 1).

3(S) 3-(1,2-Dihydro-2-oxo-6-phenethyl-3(3-phenylpropionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54c), was isolated (46%) as a white solid: IR (KBr) 3375, 1694, 1643, 1586, 1561, 1515, 1377, 1254, 1188, 1070; ¹H NMR (CD₃OD) 8.18 (1H, d, J=7.8), 7.22 (10H, m), 6.15 (1H, d, J=7.8), 4.75 (2H, s), 4.58 (1H, m), 4.30 (1H, m), 3.01-2.28 (10H, m); MS FAB+ M+ = 504 (M + 1).

- 195 -

3(S) 3-(6-Butyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54d), was isolated (90%) as colorless crystals: m.p. 120-5°C; IR (KBr) 3315, 1784, 1679, 1644, 1589, 1561, 1556, 1520, 1415, 1379, 1186; ¹H NMR (CD₃OD) 8.22 (1H, d, J=7.8), 7.24 (5H, m), 6.22 (1H, d, J=7.8), 4.80 (2H, m), 4.60 (1H, s), 4.28 (1H, m), 2.98 (2H, m), 2.72 (2H, m), 2.58 (4H, m), 1.48 (4H, m), 0.97 (3H, t, J=7.1). Anal. Calcd for C₂₄H₂₉N₃O₆ 0.5 H₂O. C, 62.06; H, 6.51; N, 9.05. Found: C, 62.08; H, 6.43; N, 9.01. MS FAB+ M+ = 456 (M + 1).

3(S) 3-(1,2-Dihydro-6-methyl-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54e), was isolated (85%) as a colorless solid: mp. 129-138°C; IR (KBr) 327, 3294, 1710, 1695, 1682, 1554, 1525, 1379, 1272, 1240; ¹H NMR (CD₃OD) δ 8.19 (1H, d, J=7.6), 7.19 (5H, m), 6.21 (1H, d, J=7.6), 4.80 (2H, m), 4.59 (1H, m), 4.30 (1H, m), 2.98 (2H, m), 2.72 (2H, m), 2.80-2.40 (2H, m), 2.30 (3H, s). Anal. Calcd for C₂₁H₂₂N₃O₆ · H₂O: C, 58.46; H, 5.84; N, 9.74. Found C: 58.82; H, 60.5; N, 9.42.

3(S) 3-(1,2-Dihydro-2-oxo-6-phenyl-3-(3-phenylpropionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54f), 73% as an off-white solid: m.p. 140°C (decomp). [α]_D²⁴ = -8.5° (c 0.1, MeOH). IR (KBr) 3302, 1796, 1726, 1679, 1643, 1590, 1560, 1516, 1490, 1449, 1420, 1398, 1376, 1231; ¹H NMR (CD₃OD) δ 8.36 (1H, d), 7.49-7.14 (10H, m), 6.27 (1H, dd), 4.54 (3H, m), 4.30 (1H, m), 3.0, 2.73 (2 x 2H, 2 x m), 2.7-2.29 (2H, m).

3(S) 3-(1,2-Dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54g; G), was isolated (73%) as a foam: mp. 140-5°C (decomp); IR

- 196 -

(KBr) 3352, 3314, 1719, 1700, 1668, 1649, 1600, 1559, 1514, 1379, 1261; ^1H NMR (CD_3OD) δ 8.32 (1H, d, $J=7.5$), 7.19 (6H, m), 6.34 (1H, t), 5.1-4.6 (3H, m), 4.32 (1H, m), 2.7 (6H, m). Anal. Calcd for $\text{C}_{20}\text{H}_{21}\text{N}_3\text{O}_6 \cdot 0.6\text{H}_2\text{O}$: C, 58.50, H, 5.45, N, 10.24. Found: C, 58.43, H, 5.35, N, 9.85. MS FAB+ $M + = 400$ ($M + 1$).

3(S), N(2(R,S)) 3-(2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)propionylamino)-4-oxobutanoic acid (54h), was obtained (69%) as a colorless foam: m.p. 120°C ; $[\alpha]_D^{20} -16.0^\circ$ (c, 0.11, CH_2Cl_2). IR (KBr) 3315, 1783, 1727, 1666, 1644, 1599, 1564, 1517, 1454, 1379; ^1H NMR (CD_3OD) δ 8.23 (1H, m), 7.27 (10H, m), 6.28 (1H, m), 4.84 (1H, m), 4.53 (1H, m), 4.22 (1H, m), 4.10 (2H, m), 2.96 (2H, m), 2.72 (2H, m), 2.39 (2H, m), 1.21 (3H, m). Anal. Calcd for $\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}_6 \cdot 1.25\text{H}_2\text{O}$: C, 63.93, H, 6.03, N, 7.99. Found: C, 63.98, H, 5.85, N, 7.86. MS FAB (+) $M + = 504$ ($M + 1$).

3(S) 3-(3-(2-Acetyl-L-tyrosinyl)amino-6-benzyl-1,2-dihydro-2-oxo-1-pyridyl)acetylamino-4-oxobutanoic acid (54i), was isolated (79%) as colorless crystals: mp. $193-6^\circ\text{C}$ (decomp.); IR (KBr) 3284, 1644, 1599, 1565, 1519, 1455, 1429, 1407, 1375, 1267, 1251; ^1H NMR (d_6 -DMSO/ CDCl_3) δ 8.16 (1H, d, $J=7.7$), 7.26 (5H, m), 7.03 (2H, d, $J=8.4$), 6.61 (2H, d, $J=8.4$), 6.03 (1H, d, $J=7.7$), 4.58 (3H, m), 4.44 (1H, m), 4.13 (1H, m), 3.84 (2H, s), 3.07-2.30 (4H, m). Anal. Calcd for $\text{C}_{29}\text{H}_{30}\text{N}_4\text{O}_8 \cdot 2\text{H}_2\text{O}$: C, 58.19; H, 5.72; N, 9.36. Found: C, 58.11; H, 5.63; N, 9.29. MS FAB+ $M + = 563$ ($M + 1$).

3(S) 3-(6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethanesulphonyl)amino-1-pyridyl)acetylamino-4-oxobutanoic acid (54j), was isolated (85%) as a colorless solid:

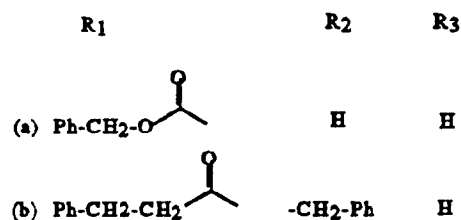
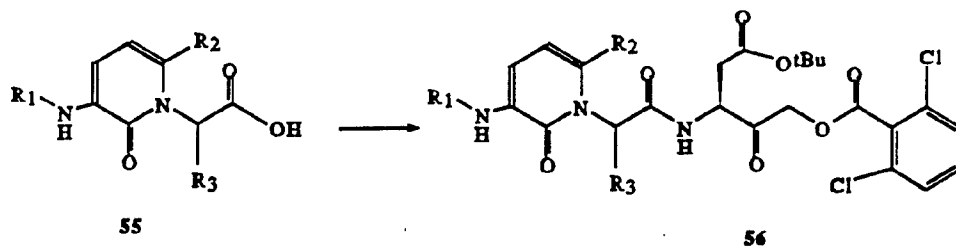
- 197 -

mp. 102-5°C; $[\alpha]_D^{23}$ -9.9° (c 0.1, MeOH); IR (KBr) 3452, 3328, 3155, 1719, 1679, 1645, 1594, 1567, 1453, 1425, 1357, 1307, 1225, 1148, 1132; ^1H NMR (CD_3OD) δ 7.52 (1H, d, $J=7.6$), 7.33 (10H, m), 6.12 (1H, d, $J=7.6$), 4.73 (2H, m), 4.58 (1H, d, $J=3.7$), 4.34 (1H, m), 3.97 (2H, s), 3.29 (2H, m), 3.08 (2H, m), 2.75-2.37 (2H, m).
5 Anal. Calcd for $\text{C}_{26}\text{H}_{27}\text{N}_3\text{O}_7\text{S} \cdot 1.7\text{H}_2\text{O}$: C, 56.14; H, 5.51; N, 7.55. Found: C, 56.20; H, 5.49; N, 7.29. MS FAB+ $M^+ = 526$ ($M + 1$).

10 3(S) 3-(6-Benzyl-1,2-dihydro-2-oxo-3-(2-phenylethoxy)carbonylamino-1-pyridyl)acetylamino-4-oxobutanoic acid (54k), was isolated (54%) as an off-white solid: mp. 84-86°C; IR (KBr) 3373-3310, 1787, 1726, 1691, 1649, 1599, 1567, 1517, 1367, 1215; ^1H NMR (CD_3OD) δ 7.93 (1H, bd, $J=7.4$), 7.37-7.18 (10H, m), 6.15 (1H, d, $J=7.4$), 4.77 (1H, d, $J=3.7$), 4.67 and 4.58 (2H, 2m), 4.35 (2H, t, $J=6.9$), 4.35 (1H, m), 3.94 (2H, s), 2.98 (2H, t, $J=6.9$), 2.76-2.39 (2H, m).
15

20 3(S) 3-(6-Benzyl-1,2-dihydro-2-oxo-3-(4-phenylbutyryl)carbonylamino-1-pyridyl)acetylamino-4-oxobutanoic acid (54l), was isolated (50%) as a white solid: mp. 89-93°C; IR (KBr) 3369-3302, 1678, 1645, 1594, 1565, 1517, 1379, 1258; ^1H NMR (d_4 -methanol) δ 8.25 (1H, d, $J=7.6$), 7.37-7.18 (10H, m), 6.15 (1H, d, $J=7.4$), 4.74 (2H, m), 4.60 (1H, m), 4.30 (1H, m), 3.97 (2H, s), 2.76-2.37 (2H, m), 2.67 (2H, t), 2.45 (2H, t), 1.98 (2H, m). Anal. Calcd for $\text{C}_{28}\text{H}_{29}\text{N}_3\text{O}_6 \cdot 1.5\text{H}_2\text{O}$: C, 63.39; H, 6.08; N, 7.92. Found C: 63.69; H, 5.74; N, 7.83.
25

- 198 -

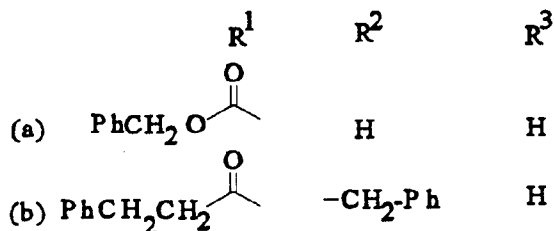
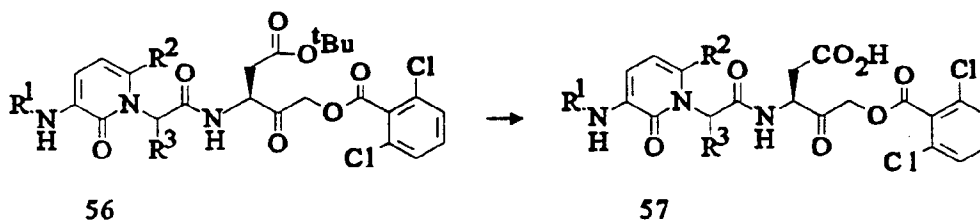


t-Butyl N-2-(3-benzyloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoate (56a). The acetic acid (55a) (WO 93 21213) in THF (2ml) was stirred at room temperature and treated with 1-hydroxybenzotriazole (60mg, 0.448mmol) and dimethylaminopropyl-3-ethylcarbodiimide hydrochloride (47mg, 0.246mmol). After 5 mins water (2 drops) was added and stirring continued for 20 minutes. Bis(triphenylphosphine) palladium II chloride (6mg) was added followed by a solution of t-butyl 3-(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyl-oxy)pentanoate (WO 93 16710) (103mg, 0.224mmol) in THF (1ml). Tributyltin hydride (0.09ml, 0.336mmol) was added dropwise over 1 hour at room temperature. The mixture was stirred for a further 3 hours and poured onto ethyl acetate, washed with 1M HCl, aqueous NaHCO₃, brine, dried over MgSO₄ and concentrated in vacuo. The residue was triturated with pentane and the supernatant discarded. The remaining solid was purified by flash chromatography (50% ethyl acetate/hexane) to afford the title compound 92mg (63%)

- 199 -

as a colorless oil: $[\alpha]_D^{26} -29.6^\circ$ (c 1.1, CH_2Cl_2); IR (film) 3377, 3365, 3332, 3312, 1733, 1691, 1650, 1599, 1515, 1366, 1261, 1153, 1068, 747; ^1H NMR (CDCl_3) δ 8.09 (1H, d, $J = 6.8$), 7.84 (1H, s), 7.58 (1H, d, $J = 8.3$), 7.33 (8H, m), 7.02 (1H, dd, $J = 6.9, 1.7$), 6.33 (1H, t, $J = 7.2$), 5.20 (2H, s), 5.12 (2H, m), 4.89 (1H, dt), 4.65 (2H, m), 2.80 (2H, m), 1.38 (9H, s).

t-Butyl N-2-(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzyloxy)-4-oxo-pentanoate (56b), was prepared by the method described for (56a) which afforded the title compound (66%) as a colorless oil: IR (film) 3364, 3313, 1738, 1688, 1648, 1600, 1566, 1514, 1433, 1369, 1254, 1152; ^1H NMR (CDCl_3) δ 8.40 (1H, d, $J = 7.6$), 8.30 (1H, s), 7.28 (13H, m), 6.20 (1H, d, $J = 7.6$), 5.12 (2H, q), 4.86 (1H, m), 4.65 (2H, q), 4.06 (2H, s), 3.07-2.61 (6H, m), 1.39 (9H, s).

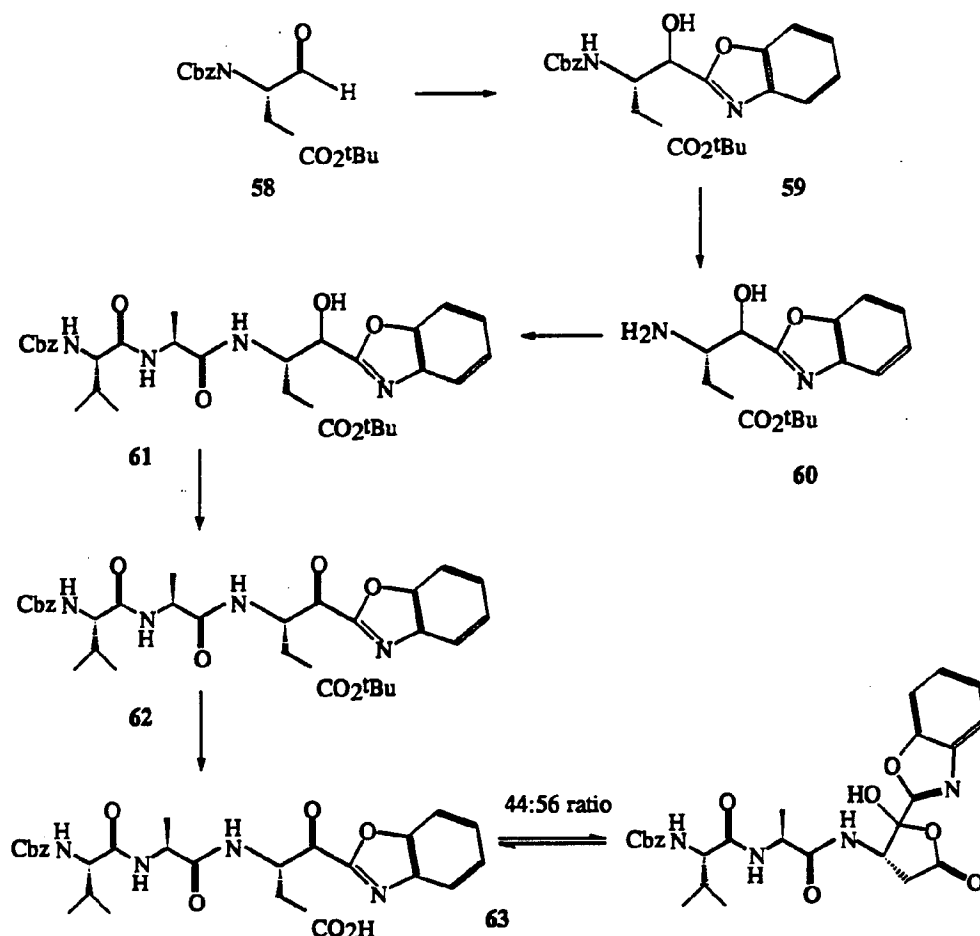


- 200 -

N-2(3-Benzylloxycarbonylamino-1,2-dihydro-2-oxo-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (57a; Q). The ester (56a) (210mg, 0.356mmol) in dichloromethane (0.5ml) was cooled to 0°C and treated with trifluoroacetic acid (0.5ml), stirred and warmed to 20°C over 30 minutes. The solution was evaporated to dryness under reduced pressure, redissolved in dichloromethane and concentrated (x3). The residue was triturated with ethyl acetate and diluted with ether to afford the title compound 162mg (85%) as a colorless solid: m.p. 165-8°C (decomposition); $[\alpha]_D^{23}$ -38.8° (c 0.1, CH₃OH); IR (KBr) 3332, 3275, 1723, 1658, 1649, 1597, 1581, 1562, 1526, 1432, 1385, 1258, 1218, 1206; ¹H NMR (d₆-DMSO) δ 8.96 (1H, d, J = 7.3), 8.34 (1H, s), 7.85 (1H, dd, J = 7.3), 7.58 (3H, m), 7.35 (5H, m), 6.29 (1H, t, J = 7.3), 5.26 (2H, m), 5.15 (2H, s), 4.69 (3H, m), 2.75 (2H, m). Anal. Calcd. C₂₇H₂₃N₃O₉Cl₂: C, 53.66; H, 3.84; N, 6.95. Found: C, 53.36; H, 3.90; N, 6.81. M.S. (+ FAB); 604 (M⁺ + 1), 285, 241, 195, 173, 149, 91.

N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3-amino-5-(2,6-dichlorobenzoyloxy)-4-oxo-pentanoic acid (57b; P), was prepared by the method described for 57a which afforded the title compound (78%) as colorless crystals: m.p. 116-120°C (decomposition); $[\alpha]_D^{26}$ -41.1° (c 0.1, CH₃OH); IR (KBr) 3299, 1739, 1715, 1689, 1666, 1645, 1598, 1563, 1518, 1432, 1209, 1151; ¹H NMR (d₆-DMSO) δ 9.24 (1H, s), 8.88 (1H, d, J = 7.6), 8.18 (1H, d, J = 7.7), 7.60 (3H, m), 7.26 (10H, m), 6.06 (1H, d, J = 7.7), 5.23 (2H, ABq), 4.69 (3H, m), 3.93 (2H, s), 2.78 (6H, m). Anal. Calcd. for C₃₅H₃₁N₃O₈Cl₂ · H₂O: C, 59.16; H, 4.68; N, 5.91. Found: C, 59.38; H, 4.53; N, 5.84. M.S. (+ FAB); 694, (Cl=35, 37), (M⁺ + 1); 692 (Cl=35, 35), (M⁺ + 1).

- 201 -



(3*S*, 4*R*, *S*) *t*-Butyl *N*-(benzyloxycarbonyl)-3-amino-4-(2-benzoxazolyl)-4-hydroxy-butanoate (59). To a stirred solution of benzoxazole (250.2mg, 2.1mmol) in anhydrous THF (10.5ml) at -78°C under N₂ was added 2.3M *n*-butyl lithium in hexanes (0.96ml, 2.2mmol) dropwise. After stirring at -78°C for 20min, dry MgBr₂OEt₂ (594.0mg, 2.3mmol) was added as a solid. The resulting heterogeneous mixture was warmed to -45°C and stirred for 15min. The reaction mixture was then recooled to -78°C and a solution of aldehyde 58 (Graybill et al., Int. J. Peptide Protein Res., 44, pp. 173-182 (1993)) (644.6mg, 2.1mmol) in THF (10.5ml) was added dropwise.

- 202 -

The reaction was stirred at -78°C for 30min, warmed to 0°C for 1h, and then stirred at room temperature for 16h. The reaction was quenched with 5% sodium bicarbonate (2.0ml) and the THF was removed in vacuo. The resulting aqueous residue was extracted four times with methylene chloride. The combined extracts were washed with brine, dried (MgSO₄), filtered and reduced in vacuo to give 880.0mg of crude product. Flash chromatography (45:55 ethyl acetate/hexane) afforded 567.2mg (63%) of the title compound, an oil, as a mixture of diastereoisomers at C-4. IR (film) 3324, 2976, 1726, 1517, 1455, 1368, 1243, 1159, 1048, 747; ¹H NMR (CDCl₃) δ 7.71-7.64 (1H, m), 7.52-7.48 (1H, m), 7.37-7.20 (7H, m), 5.91 (1H, brd, *J* = 9.0), 5.79 (1H, d, *J* = 9.0), 5.41-4.78 (4H, m), 4.75-4.54 (1H, m), 2.91-2.51 (2H, m), 1.42 (9H, s), 1.37 (9H, s).

(3*S*, 4*R*, *S*) *t*-Butyl 3-amino-4-(2-benzoxazolyl)-4-hydroxybutanoate (60). A solution of the ester 59 (189.0mg, 0.44mmol) in ethanol (5.0ml) was treated with 10% Palladium on carbon (20.5mg) and stirred under an atmosphere of H₂ for 21h. The mixture was filtered through Celite®, and the solvent was evaporated to afford 125.0mg (98%) of crude amine 60 as an oil. This was used without further purification. ¹H NMR (CDCl₃) δ 7.73-7.64 (1H, m), 7.51-7.42 (1H, m), 7.35-7.22 (2H, m), 6.48 (3H, brs), 5.58 (1H, d, *J* = 3.0), 5.27 (1H, d, *J* = 6.5), 4.23-4.05 (1H, m), 2.92-2.63 (2H, m), 1.36 (9H, s), 1.33 (9H, s).

(3*S*, 4*R*, *S*) *t*-Butyl *N*-(*N*-benzyloxycarbonyl-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-(2-benzoxazolyl)-4-hydroxybutanoate (61). A solution of the amine 60 (261.4mg, 0.89mmol), *Z*-Val-Ala-OH (286.9mg, 0.89mmol) (prepared by standard peptide synthetic procedures) and

- 203 -

hydroxybenzotriazole (120.3mg, 0.89mmol) in DMF (3.0ml) at 0°C was treated with 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (179.2mg, 0.93mmol). The reaction was warmed to room temperature and stirred for 16h. The reaction was diluted with ethyl acetate and washed twice with 1M sodium hydrogensulphate, twice with saturated sodium bicarbonate, then water, and brine. The organic layer was dried (MgSO₄), filtered and reduced in vacuo to afford 494.8mg of crude product. Flash chromatography (95:5 methylene chloride/methanol) gave 480.9mg (91%) of the title compound as a yellow solid: mp. 81-83°C; IR (KBr) 3312, 2974, 1723, 1709, 1529, 1455, 1368, 1243, 1156, 747; ¹H NMR (CDCl₃) δ 7.79 (0.5H, d, *J* = 8.0), 7.73-7.20 (9.5H, m), 6.15 (1H, t, *J* = 8.5), 5.74 (0.5H, brd, *J* = 5.5), 5.45 (1H, brd, *J* = 7.5), 5.28-5.20 (0.5H, m), 4.82-4.11 (3.5H, m), 4.78-4.55 (1H, m), 4.40-4.22 (1H, m), 2.95-2.51 (2H, m), 2.12-1.95 (1H, m), 1.45-1.32 (12H, m), 1.11-0.81 (6H, m), ¹³C NMR (CDCl₃) δ 173.14, 172.94, 171.82, 171.03, 170.78, 165.98, 165.45, 157.29, 157.17, 151.23, 151.10, 140.92, 140.82, 136.83, 136.79, 128.91, 128.52, 125.75, 124.97, 120.60, 120.40, 111.38, 81.82, 81.68, 70.27, 68.97, 67.44, 60.43, 50.74, 50.55, 49.18, 49.07, 36.87, 36.57, 32.37, 28.51, 19.88, 19.80, 18.53. Anal. Calcd. for C₃₁H₄₀N₄O₈. H₂O: C, 60.57; H, 6.89; N, 9.11. Found: C, 60.84; H, 6.64; N, 9.09. M.S. (+ FAB); 597 (M⁺ + 1); 541, 91.

(3*S*) t-Butyl N-(N-benzyloxycarbonyl-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-(2-benzoxazolyl)-4-oxobutanoate (62). The alcohol 61 (100.3mg, 0.17mmol) was dissolved in methylene chloride (2.0ml) and Dess-Martin reagent (142.6mg, 0.34mmol) was added (Ireland et al., J. Org. Chem., 58, p. 2899 (1993); Dess et al., J. Org. Chem., 48, pp. 4155-4156 (1983)). The resulting mixture was

- 204 -

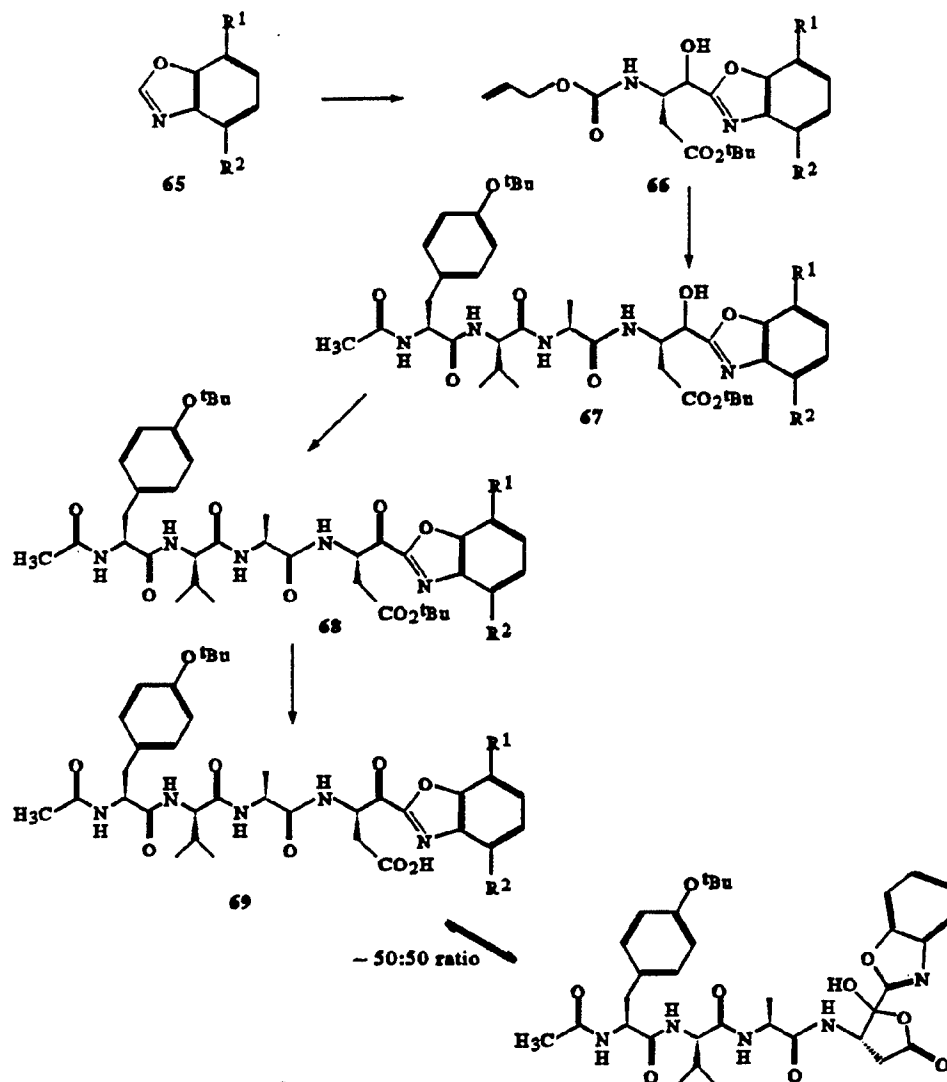
stirred for 22min and then partitioned between saturated sodium thiosulphate: saturated sodium bicarbonate (1:1, 10ml), and ethyl acetate (10ml). The resulting organic phase was washed with saturated sodium thiosulphate, saturated sodium bicarbonate (1:1), saturated sodium bicarbonate, and brine. The organic phase was dried (MgSO_4), filtered and reduced in vacuo to give 111.3mg of crude product. Flash chromatography (95:5 methylene chloride/methanol) afforded 97.3mg (96%) of the title compound as an oil: $[\alpha]_D^{23} -11.74^\circ$ (c 0.95, CH_2Cl_2); IR (CH_2Cl_2) 3419, 2974, 1721, 1677, 1501, 1369, 1221, 1156; ^1H NMR (CDCl_3) δ 7.89-7.84 (1H, m), 7.73-7.22 (10H, m), 5.98 (1H, d, $J = 9.0$), 5.72 (1H, m), 5.10 (2H, q, $J = 12.5$), 4.73 (2H, m), 4.20 (1H, dd, $J = 7.0, 8.5$), 3.30 (1H, dd, $J = 5.0, 16.5$), 3.03 (1H, dd, $J = 5.5, 16.5$), 2.18-1.97 (1H, m), 1.39 (3H, d, $J = 7.0$), 1.34 (9H, s), 0.93 (3H, d, $J = 6.0$), 0.90 (3H, d, $J = 6.0$), ^{13}C NMR (CDCl_3) δ 186.46, 172.73, 171.90, 170.13, 157.17, 156.28, 151.16, 140.99, 136.99, 129.39, 129.08, 128.66, 128.59, 126.49, 123.06, 112.55, 82.73, 67.60, 60.84, 53.75, 49.41, 38.58, 32.05, 28.52, 19.85, 19.32, 18.51. M.S. (+ FAB); 595 ($M^+ + 1$); 539, 91.

(3S) N-(N-Benzylloxycarbonyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-benzoxazolyl)-4-oxobutanoate (63; Q). A solution of the ester 62 (95.0mg, 0.16mmol) in a 1:1 mixture of methylene chloride and trifluoroacetic acid (10.0ml) was stirred for 1h under a dry atmosphere of N_2 . The solution was then reduced in vacuo, taken up in ether and reduced again. This process was repeated six times to afford the crude product as an off white solid. Flash chromatography (95:5 methylene chloride/methanol) gave 60.0mg (69%) of the title compound as a white solid. The product existed as a

- 205 -

mixture of three isomers in CD₃OD, consisting of the ketone form (one isomer, c 44%), and its acycloxy ketal form (two isomers at C-4, c. 56%): m.p. 156-159°C [α]_D²⁶ -45.6° (c 0.13, methanol); IR (KBr) 3440, 2967, 1713, 1703, 1638, 1531, 1427; ¹H NMR (CD₃OD) δ 7.93-7.24 (9H, m), 5.59 (1H, brt), 5.16-5.00 (2H, m), 5.0-4.78 (1H, m), 4.50-4.22 (1H, m), 3.95-3.81 (1H, m), 3.11 (2H, d, J = 6.5), 3.05-2.92 (1H, m), 2.70-2.39 (1H, m), 2.08-1.89 (1H, m), 1.19-0.78 (9H, m). Anal. Calcd. for C₂₇H₃₀N₄O₈ · 0.5H₂O: C, 59.22; H, 5.71; N, 10.23. Found: C, 59.48, H, 5.36, N, 10.17. M.S. (+ FAB); 539 (M⁺ + 1), 91.

- 206 -

(a) $R^1 = \text{OCH}_3$, $R^2 = \text{H}$ (b) $R^1 = \text{H}$, $R^2 = \text{OCH}_3$

7-Methoxybenzoxazole (65a). A mixture of 2-nitro-6-methoxyphenol (2.62g, 15.5mmol) (EP 333176) and 10% Palladium on carbon (130mg) in ethanol (50.0ml) was stirred under an atmosphere of H_2 for 75min. The mixture was filtered through Celite® then immediately treated with p-toluenesulphonic acid (32.0mg) and triethylorthoformate (6.45ml, 38.8mmol) then heated under reflux under an atmosphere of N_2 . After 20h p-

- 207 -

toluenesulphonic acid (30.0mg) and triethylorthoformate (6.45ml, 38.8mmol) were added. After a total of 44h heating, the reaction was allowed to cool and reduced in vacuo. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 1.97g (85%) of the title compound as a yellow solid: m.p. 28-31°C; IR (film) 1629, 1497, 1434, 1285, 1097; ¹H NMR (CDCl₃) δ 8.09 (1H, s), 7.40 (1H, d, J = 8.0), 7.28 (1H, t, J = 8.0), 6.89 (1H, d, J = 8.0), 4.02 (3H, s); ¹³C NMR (CDCl₃) δ 152.84, 145.82, 142.50, 139.99, 125.75, 113.42, 108.80, 56.97. Anal. Calcd. for C₈H₇N₁O₂ · 0.1H₂O: C, 63.65; H, 4.81; N, 9.29. Found: C, 63.43, H, 4.88, N, 9.05. M.S. (+ FAB); 150 (M⁺ + 1).

4-Methoxybenzoxazole (65b). To a suspension of 4-hydroxybenzoxazole (2.00g, 14.8mmol) (Musser et al., J. Med. Chem., 30, pp. 62-67 (1987)) in acetone (80.0ml) was added dried K₂CO₃ (2.25g, 16.3mmol) followed by iodomethane (1.38ml, 22.2mmol). The reaction was heated under reflux under N₂ for 4.5h, then filtered and reduced in vacuo to afford the crude product. The resulting residue was purified by flash chromatography (25:75 ethyl acetate/hexane) to give 2.0g (91%) of the title compound as a white crystalline solid: m.p. 72-74°C; IR (KBr) 3089, 1619, 1610, 1503, 1496, 1322, 1275, 1090, 1071, 780, 741; ¹H NMR (CDCl₃) δ 8.02 (1H, s), 7.32 (1H, t, J = 8.0), 7.18 (1H, d, J = 8.0), 6.81 (1H, d, J = 8.0), 4.04 (3H, s). Anal. Calcd. for C₈H₇NO₂: C, 64.42; H, 4.73; N, 9.39. Found: C, 64.40; H, 4.84; N, 9.31; m/z (EI) 149 (M⁺ + 1, 100%).

(3S, 4R,S) t-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (66a). To a stirred solution of 7-methoxybenzoxazole 65a (548.6mg, 3.68mmol) in anhydrous THF (18.5ml) at -78°C

- 208 -

under N₂ was added 1.56M *n*-butyl lithium in hexanes (2.47ml, 3.86mmol) dropwise, to produce a yellow colored solution. After stirring at -78°C for 20 min, dry MgBr₂OEt₂ (1.045g, 4.05mmol) was added as a solid.

5 The resulting heterogeneous mixture was warmed to -45°C and stirred for 15min. The reaction mixture was then recooled to -78°C and a solution of (S)-Alloc-Asp(*t*-Bu)H^{1b} (946.4mg, 3.68mmol) in THF (18.5ml) was added dropwise. The reaction was stirred at -78°C for 30min,

10 warmed to 0°C and stirred for 1h. The resulting homogeneous reaction was warmed to room temperature and stirred for 16h. The reaction was quenched with 5% sodium bicarbonate (3.5ml) then THF was removed in *vacuo*. The resulting aqueous residue was extracted

15 with methylene chloride (x6). The combined extracts were washed with brine, dried (MgSO₄), filtered and reduced in *vacuo* to give 1.8g of crude product. Flash chromatography (40:60 ethyl acetate/hexane) gave 1.21g (81%) of the title compound, an oil, as a mixture of

20 diastereoisomers at C-4: IR (CH₂Cl₂) 3425, 2983, 1725, 1504, 1290, 1157, 1101; ¹H NMR (CDCl₃) δ 7.35-7.19 (2H, m), 6.89-6.81 (1H, m), 6.00-5.57 (2H, m), 5.32-5.05 (3H, m), 4.68-4.35 (3H, m), 4.01 (3H, s), 2.86-2.59 (2H, m), 1.45 (9H, s), 1.41 (9H, s); ¹³C NMR (CDCl₃) δ

25 171.18, 171.09, 165.80, 165.30, 156.71, 156.60, 145.65, 142.76, 142.71, 140.82, 140.72, 133.23, 125.81, 125.72, 118.41, 118.21, 113.07, 112.87, 108.95, 82.16, 70.28, 69.98, 66.52, 66.39, 57.03, 52.57, 52.29, 37.83, 36.86, 28.65. Anal. Calcd. for C₂₀H₂₆N₂O₇ · 0.6H₂O: C, 57.57; H, 6.57; N, 6.72. Found: C, 57.49, H, 6.34, N, 6.60. M.S. (+ FAB); 407 (M⁺ + 1); 351, 307, 154.

30

(3*S*, 4*R*, *S*) *t*-Butyl N-(allyloxycarbonyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazoly))butanoate (66b), was prepared according to the method described for 66a

- 209 -

which afforded 1.29g (26%, 68% based on recovered starting material) of the title compound as an oil and as a mixture of diastereoisomers at C-4: IR (CH_2Cl_2) 3400, 1725, 1625, 1505, 1369, 1354, 1281, 1263, 1226, 1158, 1092, 1048; ^1H NMR (CDCl_3) δ 7.34-7.24 (1H, m), 7.16 (1H, d, $J = 8.2$), 6.79 (1H, d, $J = 7.9$), 6.00-5.50 (2H, m), 5.30-5.05 (3H, m), 4.70-4.35 (4H, m), 4.02 (3H, s), 2.90-2.45 (2H, m), 1.45-1.41 (9H, 2 x s). Anal. Calcd. for $\text{C}_{20}\text{H}_{26}\text{N}_2\text{O}_7 \cdot 0.4\text{H}_2\text{O}$: C, 58.07; H, 6.53; N, 6.77. Found: C, 58.09; H, 6.41; N, 6.63. M.S. (+ FAB); 407 ($\text{M}^+ + 1$, 88%); 351 (100).

(3*S*, 4*R*, *S*) *t*-Butyl *N*-(*N*-acetyl-(*S*)-(O-*tert*-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-hydroxy-4-(2-(7-methoxybenzoxazolyl))butanoate (67a). To a stirred solution of the benzoxazole 66a (481.9mg, 1.19mmol) and Ac-Tyr(*t*Bu)-Val-Ala-OH (586.3mg, 1.30mmol) in methylene chloride (3.5ml) and DMF (3.5ml) was added bis(triphenylphosphine) palladium (II) chloride (18.0mg), followed by tributyltinhydride (0.80ml, 2.96mmol) dropwise. Hydroxybenzotriazole (320.4mg, 2.37mmol) was added and the mixture cooled to 0°C. 1-Ethyl-3-[3-(dimethylamino)propyl]carbodiimide hydrochloride (278.2mg, 1.42mmol) was added and the mixture was allowed to warm to room temperature and stirred for 16.5h. The reaction was diluted with ethyl acetate and washed twice with 1M sodium hydrogensulphate, twice with saturated sodium bicarbonate, water, and brine. The organic layer was dried (MgSO_4), filtered and reduced in vacuo to yield 2.0g of crude product. Flash chromatography (95:5 methylene chloride/methanol) gave 844.0mg (94%) of the title compound as a white solid: m.p. 205°C; IR (KBr) 3399, 3304, 2977, 1729, 1643, 1506, 1367, 1290, 1161; ^1H NMR (d_6 -DMSO) δ 8.24-7.78 (4H, m), 7.43-7.32 (2H, m),

- 210 -

7.23 (2H, d, $J = 8.5$), 7.16-7.07 (1H, m), 6.93 (2H, d, $J = 8.5$), 6.52, 6.40 (1H, 2 x d, $J = 5.5$, $J = 5.0$), 5.03, 4.78-4.49, 4.45-4.16 (5H, brt, 2 x m), 4.05, 4.04 (3H, 2 x s), 3.08-2.35 (14H, m), 2.11-1.89 (1H, m), 1.83 (3H, s), 1.49-1.32, 1.15, 1.0-0.81 (27H, s, 2 x m, $J = 7.0$); ^{13}C NMR (d_6 -DMSO) δ 175.55, 175.18, 173.88, 173.75, 173.05, 169.23, 157.28, 148.55, 146.16, 143.21, 136.63, 133.55, 128.87, 127.17, 115.78, 111.92, 84.02, 81.50, 71.40, 61.15, 60.05, 57.79, 53.39, 51.62, 43.76, 40.52, 34.58, 32.52, 31.60, 26.35, 23.11, 22.71, 21.76. Anal. Calcd. for $\text{C}_{39}\text{H}_{55}\text{N}_5\text{O}_{10}$. $0.5\text{H}_2\text{O}$: C, 61.40; H, 7.40; N, 9.18. Found: C, 61.43; H, 7.31; N, 9.07. M.S. (+ FAB); 754 ($\text{M}^+ + 1$); 698, 338, 267.

(3*S*, 4*R*, *S*) t-Butyl N-(N-acetyl-(*S*)-(O-tert-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-hydroxy-4-(2-(4-methoxybenzoxazolyl))butanoate (67b), was prepared according to the method described for 67a which afforded 1.05g (94%) of the title compound as a fine white powder: m.p. 210-213°C (dec); IR (KBr) 3284, 2977, 1736, 1691, 1632, 1536, 1505, 1452, 1392, 1367, 1258, 1236, 1161, 1091; ^1H NMR (d_6 -DMSO) δ 8.20-7.75 (4H, m), 7.40-7.10 (4H, m), 7.00-6.80 (3H, m), 6.45, 6.34 (1H, 2 x d, $J = 5.3$, $J = 5.0$), 5.00-4.10 (5H, m), 4.00, 3.99 (3H, 2 x s), 3.00-2.25 (4H, m), 1.95 (1H, m), 1.78 (3H, s), 1.39-0.80 (27H, m). Anal. Calcd. for $\text{C}_{39}\text{H}_{55}\text{N}_5\text{O}_{10}$. $0.5\text{H}_2\text{O}$: C, 61.40; H, 7.40; N, 9.18. Found: C, 61.58; H, 7.38; N, 8.91. M.S. (+ FAB); 754 ($\text{M}^+ + 1$, 30%); 72 (100).

(3*S*) t-Butyl N-(N-acetyl-(*S*)-(O-tert-butyl-tyrosinyl)-(*S*)-valinyl-(*S*)-alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-oxobutanoate (68a). The Dess-Martin reagent (1.082g, 2.55mmol) (Ireland et al., J. Org. Chem., 58, p. 2899 (1993); Dess et al., J. Org.

- 211 -

Chem., 48, pp. 4155-4156 (1983)) was added to a stirred suspension of the alcohol 67a (641.0mg, 0.85mmol) in methylene chloride (46.0ml). The resulting mixture was stirred for 1h before being partitioned between saturated sodium thiosulphate: saturated sodium bicarbonate (1:1, 86.0ml) and ethyl acetate (86.0ml). The resultant organic phase was washed in turn with saturated sodium thiosulphate: saturated sodium bicarbonate (1:1), saturated sodium bicarbonate, and brine. The organic phase was dried (MgSO₄), filtered and reduced in vacuo to give 660.0mg of crude product. Flash chromatography (94:6 methylene chloride/methanol) gave 636.0mg (100%) of the title compound as a white solid: m.p. 209°C; $[\alpha]_D^{24}$ -21.8° (c 0.16, methanol); IR (KBr) 3395, 3294, 2977, 1722, 1641, 1535, 1505, 1161; ¹H NMR (CDCl₃) δ 8.43-8.16 (1H, m), 7.97-7.62 (2H, m), 7.49-7.14 (3H, m), 7.08-6.95 (3H, m), 6.89-6.73 (2H, m), 5.81-5.68 (1H, m), 5.16-4.86 (2H, m), 4.53 (1H, brt), 4.03 (3H, s), 3.16-2.84 (4H, m), 2.11-1.84 (4H, m), 1.46-1.14 (21H, m), 0.92-0.78 (6H, m); ¹³C NMR (CDCl₃) δ 186.28, 173.39, 171.90, 171.19, 171.03, 169.89, 156.43, 154.75, 146.32, 142.88, 140.98, 132.31, 130.54, 126.98, 124.73, 114.95, 111.42, 82.44, 78.71, 58.92, 57.20, 54.91, 53.47, 48.77, 39.43, 38.15, 32.79, 29.44, 28.60, 23.55, 20.27, 19.70, 19.34. M.S. (+ FAB); 752 (M⁺ + 1); 696, 336, 265.

(3S) t-Butyl N-(N-acetyl-(S)-(O)-tert-butyl-tyrosinyl)-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (68b), was prepared according to the method described for the ketone 68a which afforded 420mg (55%) of the title compound as a white solid: m.p. 211-213°C (dec); $[\alpha]_D^{24}$ -23.9° (c 0.82, methanol); IR (KBr) 3277, 3075, 1723, 1690, 1632, 1530, 1506, 1392, 1366, 1269, 1234, 1160,

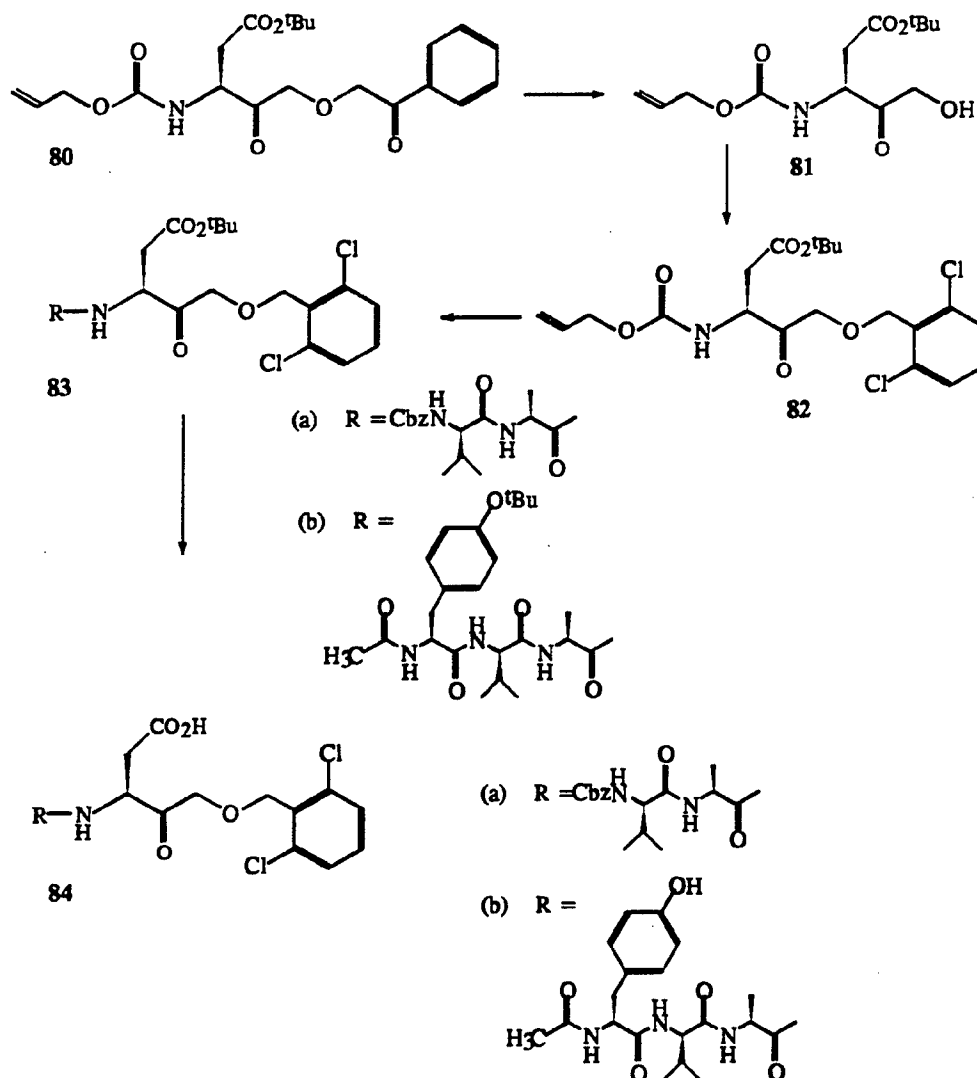
- 212 -

1094; ^1H NMR (CDCl_3) δ 8.15 (1H, brs), 7.7 (2H, brs),
7.46 (1H, t, $J = 8.3$), 7.24 (2H, d, $J = 8.3$), 7.10 (1H,
brs), 7.03 (2H, d, $J = 8.3$), 6.83 (3H, m), 5.74 (1H, q,
 $J = 6.9$), 5.00 (2H, m), 4.51 (1H, t, $J = 7.0$), 4.07
5 (3H, s), 3.20-2.95 (4H, m), 2.00 (4H, m), 1.42 (3H, d,
 $J = 6.8$), 1.35 (9H, s), 1.23 (9H, s), 0.86 (6H, d, $J =$
6.7). M.S. (+ FAB); 752 ($M^+ + 1$, 7%); 72 (100).

(3S) N-(N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-
alaninyl)-3-amino-4-(2-(7-methoxybenzoxazolyl))-4-
10 oxobutanoate (69a; R). A solution of the ester 68a
(600.0mg, 0.80mmol) in a 1:1 mixture of methylene
chloride and trifluoroacetic acid (65.0ml) was stirred
for 1h under a dry atmosphere of N_2 . The solution was
then reduced in vacuo, taken up in ether and reduced
15 again. This process was repeated six times to afford
the crude product as an off white solid. Flash
chromatography (gradient 95:5 to 80:20 methylene
chloride/methanol) gave 420.8mg (83%) of the title
compound as a hygroscopic white solid. The product
20 existed as a mixture of three isomers in CD_3OD ,
consisting of the keto form (c 50%), and its acycloxy
keto form (two isomers at C-4, c 50%): m.p. decomposes
above 150°C ; $[\alpha]_D^{24} -33.2^\circ$ (c 0.17, methanol); IR (KBr)
3300, 1715, 1658, 1650, 1531, 1517, 1204; ^1H NMR (CD_3OD)
25 δ 7.46-7.19 (2H, m), 7.16-6.91 (3H, m), 6.70-6.59 (2H,
m), 5.62-5.49 (1H, m), 5.00-4.72 (1H, obscured m),
4.69-4.51 (1H, m), 4.49-4.08 (2H, m), 4.05-3.89 (3H,
m), 3.16-2.47 (4H, m), 2.05-1.78 (4H, m), 1.41-1.11,
1.05-0.70 (9H, 2 x m). Anal. Calcd. for $\text{C}_{31}\text{H}_{37}\text{N}_5\text{O}_{10}$.
30 $3\text{H}_2\text{O}$: C, 53.67; H, 6.25; N, 10.10. Found: C, 53.76; H,
5.56; N, 10.28. M.S. (+ FAB); 640 ($M^+ + 1$); 435, 147.

- 213 -

(3S) t-Butyl N-(N-acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl)-3-amino-4-(2-(4-methoxybenzoxazolyl))-4-oxobutanoate (69b; S), was prepared according to the method described for the acid 69a which afforded the hygroscopic title compound 252mg (96%). The product existed as a mixture of three isomers in CD₃OD, consisting of the keto form, and its acycloxy ketal form (two isomers at C-4). The product existed as a single isomer in d-6 DMSO: m.p. 200-203°C (dec.); $[\alpha]_D^{24}$ -38.0° (c 0.23, methanol); IR (KBr) 3289, 2968, 1718, 1713, 1658, 1634, 1548, 1517, 1506, 1461, 1453, 1393, 1369, 1268, 1228, 1174, 1092; ¹H NMR (d₆-DMSO) δ 9.20 (1H, brs), 8.71 (1H, d, *J* = 6.2), 8.10 (2H, m), 7.83 (1H, d, *J* = 8.7), 7.61 (1H, t, *J* = 8.2), 7.46 (1H, d, *J* = 8.2), 7.08 (3H, m), 6.65 (2H, d, *J* = 8.3), 5.50 (1H, q, *J* = 6.5), 4.50 (1H, m), 4.37 (1H, m), 4.20 (1H, m), 4.05 (3H, s), 3.09-2.77 (4H, m), 1.94 (1H, m), 1.79 (3H, s), 1.23 (3H, d, *J* = 7.0), 0.82 (6H, m). Anal. Calcd. for C₃₁H₃₇N₅O₁₀ · 1.5H₂O: C, 55.85; H, 6.05; N, 10.51. Found: C, 55.21; H, 5.69; N, 10.13. M.S. (+ FAB); 640 (M⁺ + 1, 22%); 107 (100).



5

10 3S) t-Butyl N-(allyloxycarbonyl)-3-amino-4-oxo-5-(1,2-dioxo-2-phenylethyloxy)-pentanoate (80). Potassium fluoride (792mg, 13.6mmol) and then benzoyl formic acid (1.02g, 6.82mmol) were added to a stirred solution of (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-bromo-4-oxo-pentanoate (WO 93 16710) (2.17g, 6.20mmol) in dimethylformamide (30ml). The mixture was stirred for 140 mins, quenched with water (50ml) and extracted with

- 215 -

ethyl acetate (2 x 50ml). The combined organic extracts were washed with water (4 x 50ml) then brine (50ml). They were dried (MgSO_4) and concentrated to afford an oil which was purified by flash chromatography (20-45% ethyl acetate in hexane) to afford 2.44g (94%) of a colorless oil: $[\alpha]_D^{20} -35.0^\circ$ (c 1.41, CH_2Cl_2); IR (film) 3359, 2981, 2938, 1752, 1740, 1726, 1712, 1512, 1369, 1285, 1177, 1053, 991, 939, 688; ^1H NMR (CDCl_3) δ 8.15 (2H, m), 7.66 (1H, m), 7.53 (2H, m), 5.90 (2H, m), 5.33 (2H, m), 5.31 (1H, d, $J = 16.9$), 5.18 (1H, d, $J = 16.9$), 4.63 (3H, m), 3.03 (1H, dd, $J = 17.3, 4.6$), 2.74 (1H, dd, $J = 17.3, 4.9$), 1.44 (9H, s). MS (C.I.) 420 ($M^+ + 1$ 20%); 364 (100).

(3S) *t*-Butyl N-(allyloxycarbonyl)-3-amino-5-hydroxy-4-oxo-pentanoate (81). A mixture of the ester 80 (2.40g, 5.71mmol), tetrahydrofuran (200ml) and 1M aqueous potassium bicarbonate (200ml) was vigorously stirred at room temperature for 18h. The layers were separated and the aqueous portion extracted with ethyl acetate (100ml). The combined organic extracts were washed with brine (100ml), dried (MgSO_4) and concentrated. The residue was purified by flash chromatography (10-60% ethyl acetate in hexane) to afford 1.48g (90%) of pale yellow oil: $[\alpha]_D^{20} -5.9^\circ$ (c 1.06, CH_2Cl_2); IR (film) 3345, 2981, 2936, 1739, 1725, 1712, 1692, 1515, 1368, 1259, 1158, 1051; ^1H NMR (CDCl_3) δ 5.92 (2H, m), 5.30 (2H, m), 4.36-4.69 (5H, m), 3.05 (1H, dd, $J = 17.4, 4.3$), 2.93 (1H, t), 2.70 (1H, dd, $J = 17.4, 4.9$), 1.43 (9H, s). Anal. Calcd for $\text{C}_{18}\text{H}_{21}\text{N}_1\text{O}_6$. $0.25\text{H}_2\text{O}$: C, 53.51; H, 7.43; N, 4.80. Found: C, 53.61; H, 7.18; N, 4.71. MS (C.I.) 280 ($M^+ + 1$, 87%); 232 (100).

- 216 -

(3*S*) t-Butyl N-(allyloxycarbonyl)-3-amino-5-(2,6-dichlorophenyl-methoxy)-4-oxo-pentanoate (82). A stirred mixture of alcohol 81 (1.44g, 5.01mmol), 2,6-dichlorobenzyl iodide (Abraham et al., J. Chem. Soc., pp. 1605-1607 (1936)) (4.31g, 15.0mmol), silver oxide (2.32g, 10.0mmol) and dichloromethane (25ml) was heated under reflux for 45h. The mixture was allowed to cool to room temperature then diluted with water (50ml) then extracted with ethyl acetate (50ml, 25ml). The organic layer was washed with water (50ml) then brine (50ml), dried (MgSO₄), and concentrated. The residue was purified by flash chromatography (10-100% ethyl acetate in hexane) to afford 1.65g (74%) of a colorless oil: $[\alpha]_D^{20} +8.8^\circ$ (c 1.13, CH₂Cl₂); IR (film) 3339, 2980, 2935, 1724, 1712, 1503, 1438, 1368, 1246, 1156, 1106, 770; ¹H NMR (CDCl₃) δ 7.33 (2H, m), 7.22 (1H, dd), 5.92 (2H, m), 5.28 (2H, m), 4.87 (2H, m), 4.67 (1H, m), 4.58 (2H, br d), 4.56 (1H, d, *J* = 16.9), 4.31 (1H, d, *J* = 16.9), 3.04 (1H, dd, *J* = 16.7, 4.5), 2.77 (1H, dd, *J* = 16.7, 4.9), 1.40 (9H, s). Anal. Calcd. for C₂₀H₂₅Cl₂N₁O₆ · 0.25H₂O: C, 53.28; H, 5.70; N, 3.11. Found: C, 53.15; H, 5.52; N, 2.98. M.S. (C.I.); 446 (M⁺, 27%); 390 (100).

(3*R,S*) t-Butyl N-[N-phenylmethyloxycarbonylvalaninyl-alaninyl]-3-amino-5-(2,6-dichlorophenylmethoxy)-4-oxo-pentanoate (83a). 1-(3-Dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (379g, 1.98mmol) and 1-hydroxybenzotriazole (486mg, 3.60mmol) were added to a stirred solution of N-phenyl-methyloxycarbonylvalinyl-alanine (637mg, 1.98mmol) in tetrahydrofuran (40ml) and water (1ml). The mixture was stirred for 15mins and then the ether 82 (802mg, 1.80mmol) and bis(triphenylphosphine)palladium (II) chloride (ca 5mg) were added.

- 217 -

Tributyltin hydride (785mg, 725 μ l, 2.70mmol) was then added dropwise during 20mins and the resulting solution was stirred for 3.75h and then quenched with 1M hydrochloric acid (50ml). The mixture was extracted twice with ethyl acetate. The combined organic extracts were washed with 1M hydrochloric acid, twice with aqueous sodium bicarbonate, water and then brine, dried (MgSO_4) and concentrated. The residue was purified by flash chromatography (10-30% ethyl acetate - dichloromethane) to afford 941mg (79%) of pale yellow solid: m.p. 148-52°C; IR (KBr) 3287, 3070, 1730, 1691, 1641, 1536, 1369, 1289, 1247, 1156; ^1H NMR (CDCl_3) δ 7.33 (8H, m), 7.23 (1H, dd), 6.61 (1H, br, d), 5.42 (1H, br, d), 5.11 (2H, s), 4.85 (3H, m), 4.50 (1H, m), 4.40 (1H, d, $J = 16.9$), 4.26 (1H, d, $J = 16.9$), 4.02 (1H, m), 2.99 (1H, dd, $J = 16.8, 4.7$), 2.73 (1H, dd, $J = 16.8, 5.0$), 2.09 (1H, m), 1.37 (12H, m), 0.96 (3H, d, $J = 6.9$), 0.91 (3H, d, $J = 6.8$). Anal. Calcd. for $\text{C}_{32}\text{H}_{41}\text{Cl}_2\text{N}_3\text{O}_8 \cdot 0.25\text{H}_2\text{O}$: C, 57.25; H, 6.23; Cl, 10.57; N, 6.26. Found: C, 57.18; H, 6.23; Cl, 10.58; N, 5.95. M.S. (+ FAB); 667 (M^+ 1, 1%); 666 (3), 159 (25), 91 (100).

(3R,S) t-Butyl N-[(N-acetyl-O-t-butyltyrosinyl)-valaninyl-alaninyl]-3-amino-5-(2,6-dichlorophenylmethyloxy)-4-oxo-pentanoate (83b), was prepared by the method described for 83a to afford 554mg (64%) of colorless solid: m.p. 184-6°C; IR (KBr) 3282, 3075, 1736, 1690, 1633, 1536, 1508, 1366, 1236, 1161; ^1H NMR (d_6 -DMSO) δ 8.49 (1H, d), 8.14 (1H, d), 8.08 (1H, d), 7.84 (1H, d), 7.43 (3H, m), 7.14 (2H, d), 6.83 (2H, d), 4.71 (2H, s), 4.51 (2H, m), 4.36 (2H, dd), 4.17 (2H, m), 2.93 (1H, m), 2.73 (1H, m), 1.94 (1H, m), 1.74 (3H, s), 1.37 (9H, s), 1.23 (12H, m),

- 218 -

0.83 (6H, m). M.S. (+ FAB); 793 (M^+ 1, 4%); 737 (5), 681 (1), 178 (40), 159 (45), 136 (100), 107 (40). M.S. (- FAB); 792 (20), 791 (40), 447 (100).

(*R,S*) N-[N-(Phenylmethyloxy)carbonyl-valinyl-alaninyl]-
5 3-amino-5-(2,6-dichlorophenylmethyloxy)-4-oxo-pentanoic
acid (84a; **Y**). Trifluoroacetic acid (5ml) was added to
a stirred solution of the ester 83a, (918mg, 1.38mmol)
in dichloromethane (20ml). The mixture was stirred for
2.5h then evaporated to dryness. The residue was
10 treated with ether (25ml) and evaporated to dryness.
This procedure was repeated three times. The resulting
product was triturated with ether (10ml) and then dried
to afford 730mg (87%) of light brown powder: m.p. 156-
60°C; IR (KBr) 3282, 2965, 1702, 1694, 1642, 1536,
15 1438, 1246, 1230; ^1H NMR (d_6 -DMSO) δ 8.48 (1H, d), 8.09
(1H, d), 7.47 (9H, m), 5.02 (2H, s), 4.70 (2H, s), 4.49
(1H, m), 4.37 (2H, dd), 4.27 (1H, m), 3.88 (1H, m),
2.75 (1H, dd), 2.54 (1H, dd), 1.96 (1H, m), 1.19 (3H,
s), 0.84 (6H, m). Anal. Calcd. for $\text{C}_{28}\text{H}_{33}\text{Cl}_2\text{N}_3\text{O}_8 \cdot 0.5\text{H}_2\text{O}$:
20 C, 54.27; H, 5.53; Cl, 11.45; N, 6.78. Found: C,
54.49; H, 5.39; Cl, 11.33; N, 6.73. M.S. (+ FAB); 610
(M^+ 1, 10%); 91 (100).

(*R,S*) N-[N-(Acetyl)tyrosinyl-valinyl-alaninyl]-3-amino-
25 5-(2,6-dichlorophenylmethyloxy)-4-oxo-pentanoic acid
(84b; **W**), was obtained as a colorless powder (95%) by
the method used for 84a. m.p. 165-8°C: IR (KBr) 3295,
2968, 1733, 1642, 1517, 1438, 1231, 1105; ^1H NMR (d_6 -
DMSO) 9.2 (1H, br, s), 8.48 (1H, br, d), 8.14 (1H,
br, d), 8.02 (1H, br, d), 7.81 (1H, br, d), 7.45 (3H,
30 m), 7.02 (2H, d), 6.62 (2H, d), 4.70 (2H, s), 4.12-4.53
(3H, m), 3.60 (3H, m), 2.51-2.92 (4H, m), 1.96 (1H, m),
1.75 (3H, s), 1.21 (3H, d), 0.83 (6H, m). Anal. Calcd.

- 219 -

for $C_{31}H_{38}Cl_2N_4O_9 \cdot H_2O$: C, 53.22; H, 5.76; Cl, 10.14; N, 8.09. Found: C, 53.33; H, 5.54; Cl, 10.02; N, 7.85. M.S. (+ FAB); 682 (M^+ 2, 30%); 681 (67), 158 (100). (- FAB); 680 (45), 679 (100).

5

Example 6

We obtained inhibition constants (K_i) and IC_{50} values for several compounds of this invention using enzyme assays with UV-visible substrate, fluorescent substrate, and cell assays as described in Example 2.

10 The following K_i and IC_{50} values were determined for compounds 22e, 54b, 54j, 54k, 57b, 85, 86, 87, 88, 89, 90, 91, 92, 98, 102a-c, 106a-c, 108a-c, 114a, 114b, 115, 121, 125a, 125b, 126, 127, 128, 129, 130, 131, 132a, 132b, 133, 135a, 135b, 136, 137, 138, 139, 140, 15
141, 142, 144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154, 155, 156, 157, 158, 159, 160, 161, 162, and 163 using the indicated assays. The structures of compounds 22e, 54b, 54j, 54k, and 57b are shown in Example 5. The other compound structures are shown in
20 Example 7.

	<u>Compound</u>	<u>Assay</u>	
		<u>UV-visible</u> K_i (μM)	<u>Cell</u> IC_{50} (μM)
25	22e	0.19	>20
	54b		20
	54j		10
	54k		6.6
	57b		2.2
30	85	0.0035	9.8

- 220 -

	86	0.175	4.0
	87	7.2	35.0
	88	0.9	
	89	0.018	
5	90	0.42	6.2
	91	0.26	>25
	92	3.8	
	98	0.535	4.0
	102a		4.0
10	102b	0.29	1.75
	102c	0.68	
	106a	2.3	30.0
	106b	0.2	2.9
	106c	3.8	>30.0
15	108a		17.5
	108b	0.4	25.0
	108c	0.43	
	114a	0.12	3.8
	114b	3.7	
20	115	0.345	6.0
	121	4.3	
	125a	0.39	>30.0
	125b	0.060	0.30
	126	0.45	1.5
25	127	0.39	8.0
	128	0.04	7.5
	129	0.59	25.0
	130		1.20
	131	12.0	30.0
30	132a	5.0	>30.0
	132b	12.5	
	133	50.0	>30.0
	135a	0.090	0.90
	135b	0.32	0.95

- 221 -

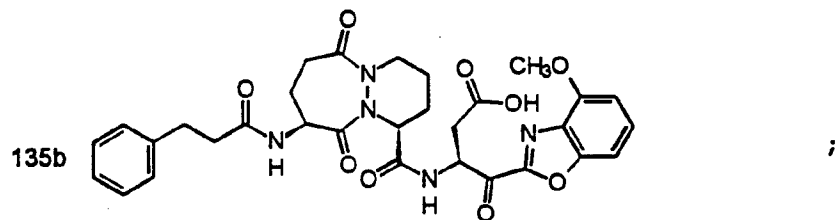
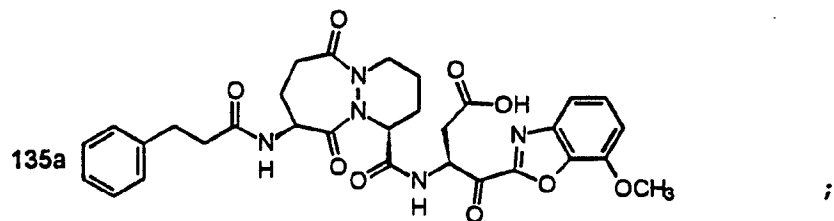
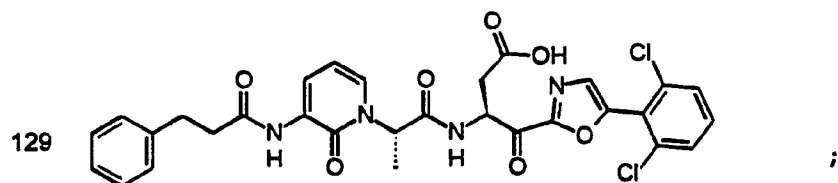
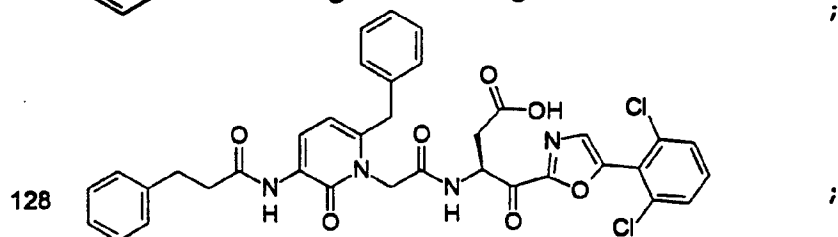
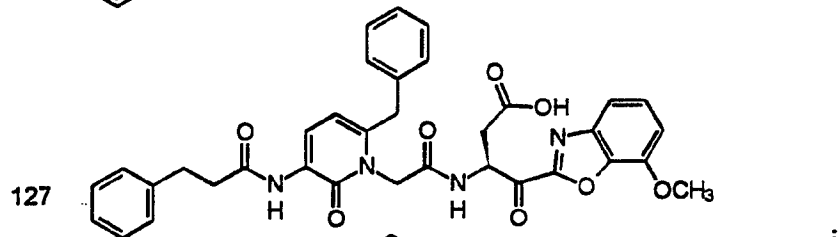
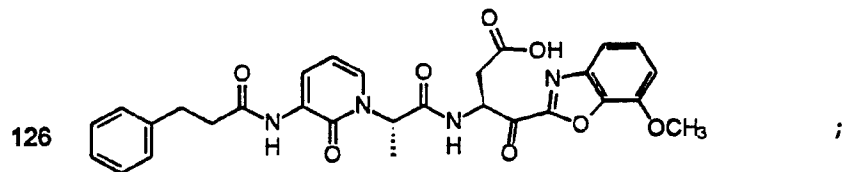
	136		1.0
	137	0.04	0.25
	138		0.375
	139	0.350	2.0
5	140	0.87	>30.0
	141	0.670	
	142		1.75
	144	0.32	>20.0
	145	0.34	8.5
10	146	0.16	3.8
	147	0.26	8.5
	148	6.3	30.0
	149	14.0	>30.0
	150	10.0	30.0
15	151	13.0	30.0
	152	8.8	
	153	0.24	
	154	0.042	2.4
	155	0.023	
20	156	0.001	2.7
	157	0.26	
	158	1.1	
	159	0.0017	8.0
	160	0.145	2.25
25	161	0.011	
	162	0.0025	
	163	0.0028	1.2

Example 7

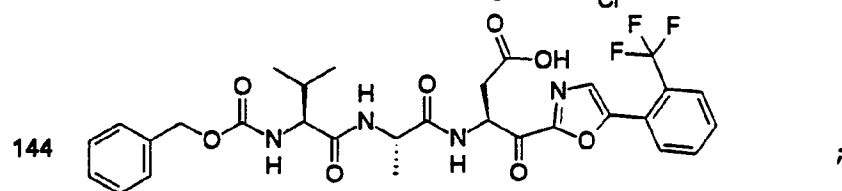
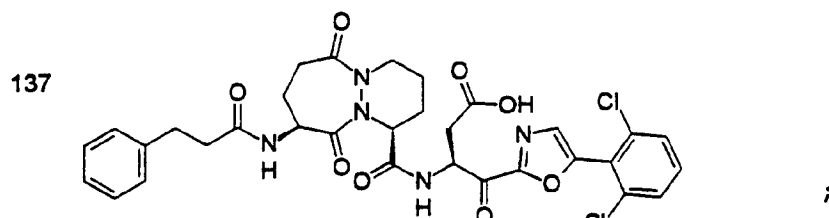
30 Compounds 126, 127, 128, 129, 135a, 135b, 137
144, 145, 146, 147, 148, 149, 150, 151, 152, 153, 154,
155, 156, 157, 159, 160, 162, and 163 were synthesized

- 222 -

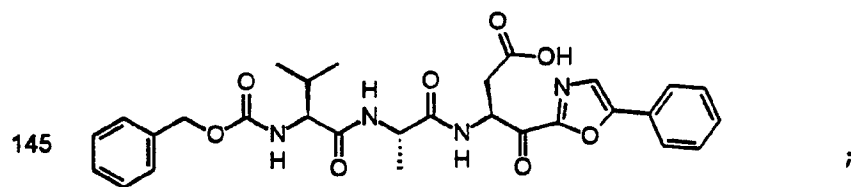
by a method similar to the method used in the synthesis of 69a.



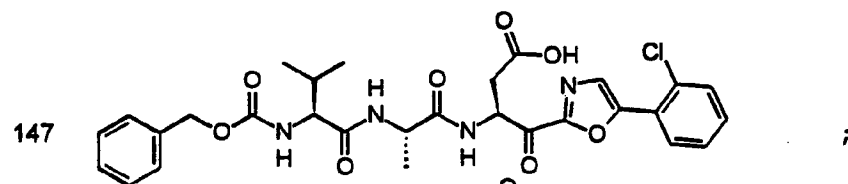
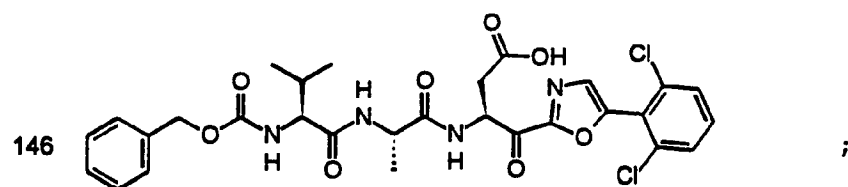
- 223 -



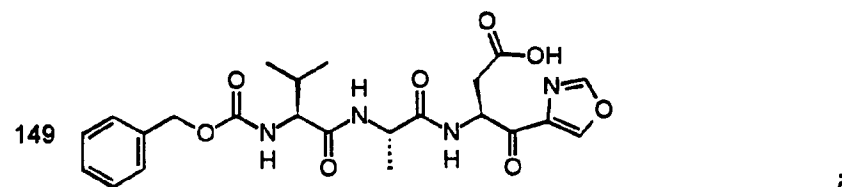
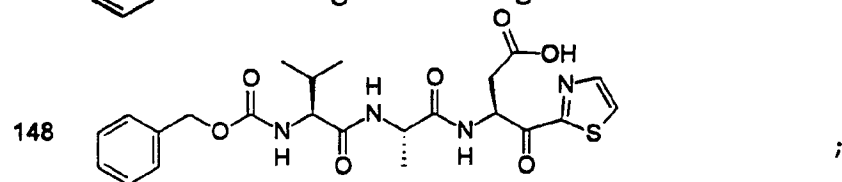
5



10

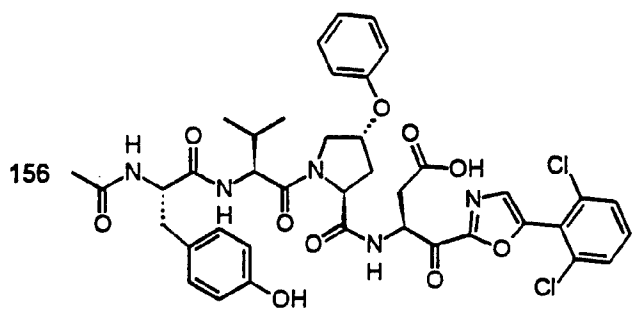
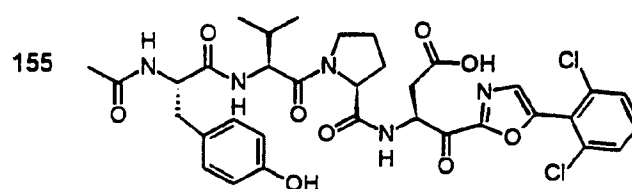
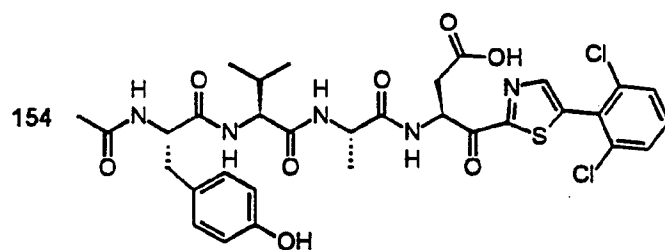
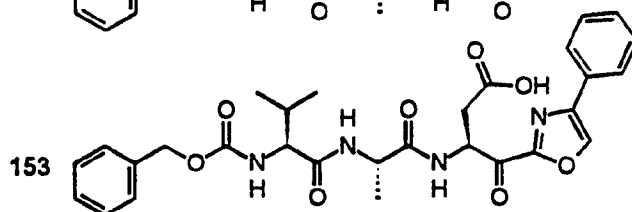
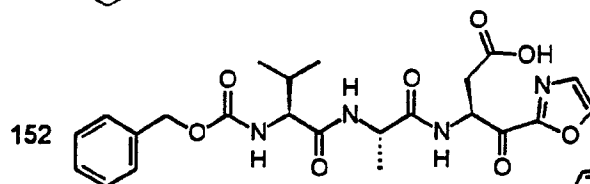
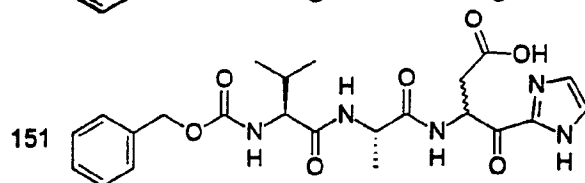
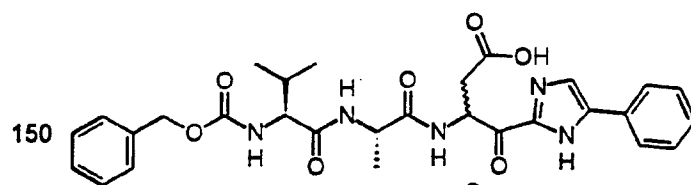


15

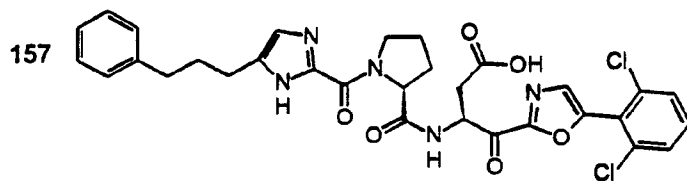


20

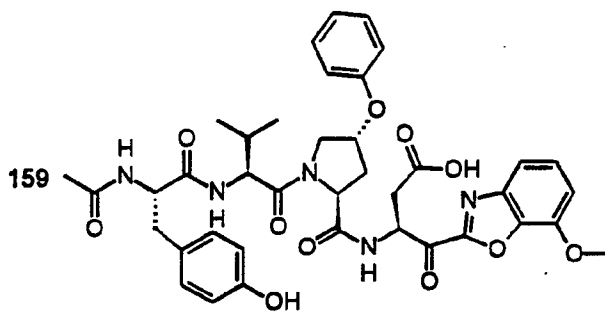
- 224 -



- 225 -

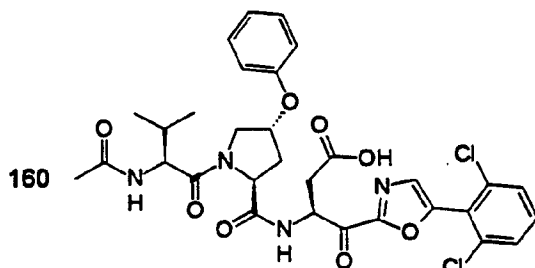


;

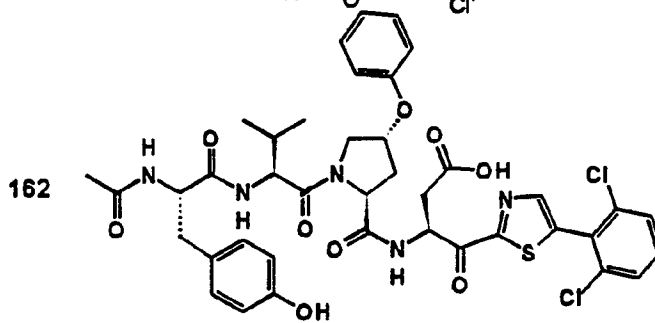


;

5

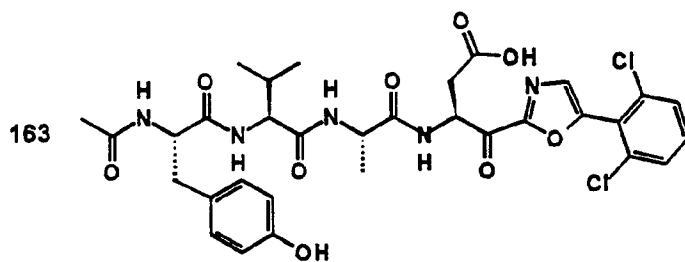


;



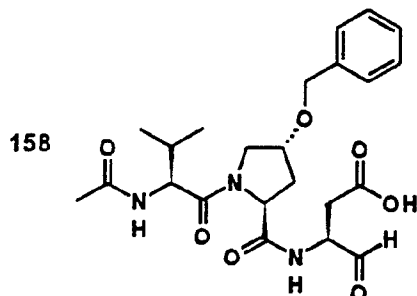
; and

10

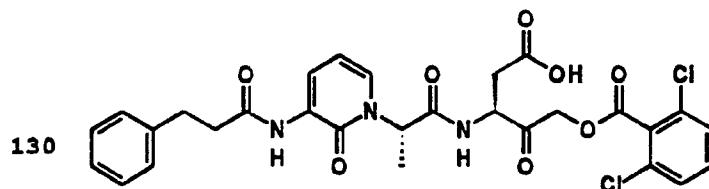


- 226 -

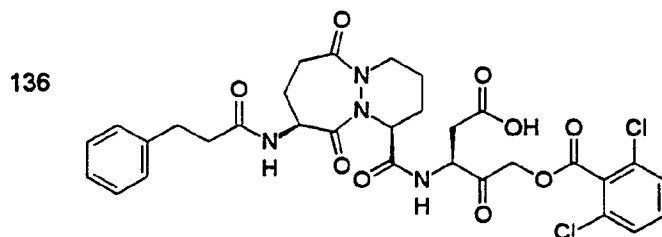
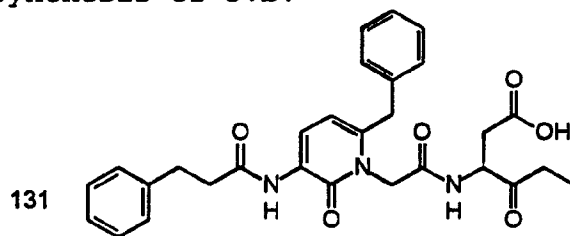
Compound 158 was synthesized by a method similar to the method used in the synthesis of (K).



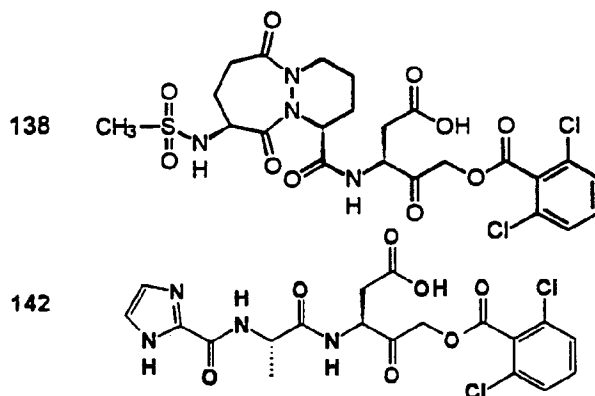
Compound 130 was synthesized by a method similar to the method used in the synthesis of 56b.



5 Compounds 131, 136, 138, and 142 were synthesized by a method similar to the method used in the synthesis of 57b.

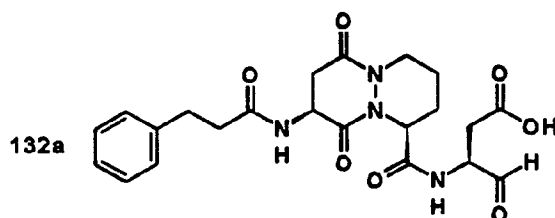


- 227 -

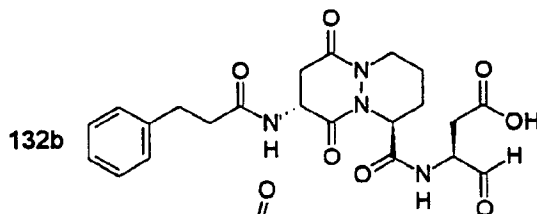


; and

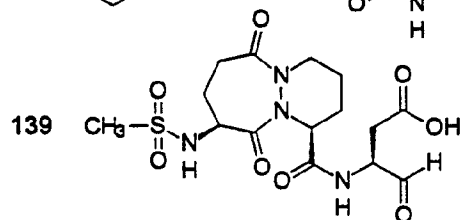
5 Compounds 132a, 132b, 139, 140, and 141 were
 synthesized by a method similar to the method used in
 the synthesis of 47a. The starting material for
 compound 140 was obtained as described in: Robl, et
 al., J. Am. Chem. Soc., 116, pp. 2348-2355 (1994). The
 10 starting material for compound 141 was obtained as
 described in: Wyvratt, et al., Pept. Struct. Funct.
Proc. (8th Am. Pept. Symp.), (1983) or USP 4415496.



;



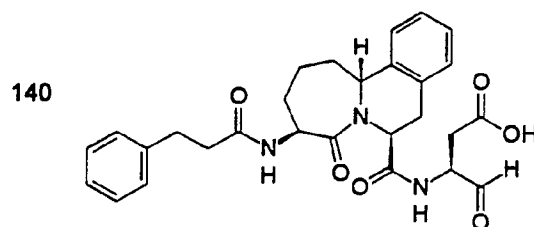
;



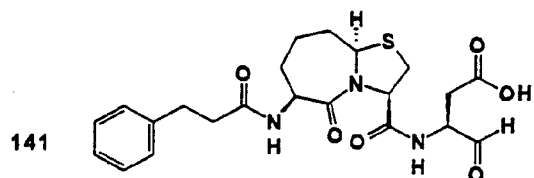
;

15

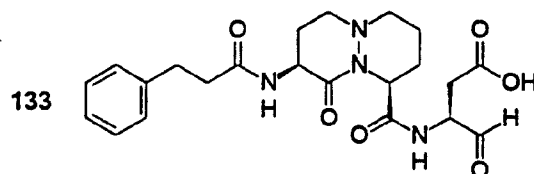
- 228 -



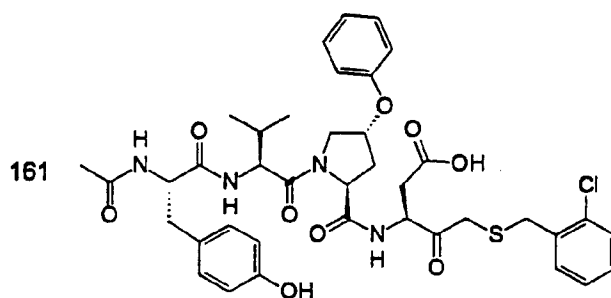
; and



Compound 133 was synthesized by a method
5 similar to the method used in the synthesis of 47b.



Compound 161 was synthesized by a method
similar to the method used in the synthesis of 125a.

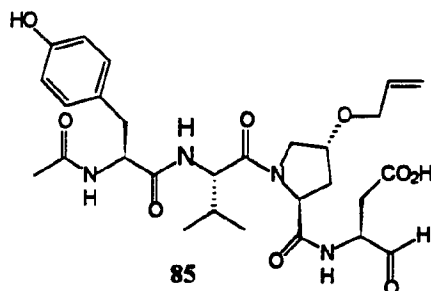


10

Compounds 22e, 54b, 54j, 54k, and 57b were
synthesized as described in example 5.

- 229 -

Compounds 85, 86, 87, 88, 89, 90, 91, 92, 98, 102a, 102b, 102c, 106a, 106b, 106c, 108a, 108b, 108c, 114a, 114b, 115, 121, 125a, and 125b were synthesized as follows.



- 5 **N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxy prolinyl))-3(S)-amino-4-oxobutanoic acid (85).**
Step A. N-tert-Butoxycarbonyl-4(R)-allyloxyproline. N-tert-Butoxycarbonyl(4R)-hydroxyproline (9.25 g, 40 mmol) was added to a
10 solution of 60% sodium hydride (3.36 g, 84 mmol) in 100 ml of anhydrous tetrahydrofuran and stirred for 2 hours at room temperature. Allyl bromide (6.9 ml, 80 mmol) was added to the mixture and refluxed for 6 hours. The mixture was quenched with the addition of
15 ice chips, then additional water was added and the mixture was washed with hexane. The aqueous layer was acidified with 10% sodium hydrogen sulfate and extracted with ethyl acetate (2 x 150 ml). The combined extracts were dried over anhydrous sodium
20 sulfate, filtered and evaporated to give 5 g of the title product with no further purification.
- ¹H NMR (CDCl₃; exist as rotamers) δ 5.92-5.82 (1H, m), 5.3-5.14 (2H, m) 4.5-4.31 (1H, m), 4.16-4.05 (1H, m), 4.04-3.9 (1H, m), 3.79-3.5 (3H, m), 2.43-2.2 (1.5H, m), 2.15-2.10 (0.5H, m), 1.45 (4.5H, s), 1.35 (4.5H, s).
- 25

- 230 -

Step B. **4(R)-Allyloxyproline methyl ester hydrochloride.** N-tert-Butoxycarbonyl-4(R)-allyloxyproline (5 g, 18.4 mmol) was refluxed in 50 ml of saturated methanolic hydrogen chloride for 6 hours. The mixture was evaporated in vacuo to give 3.78 g of a yellow gum as the title compound: ¹H NMR (CDCl₃) δ 5.83-5.72 (1H, m), 5.24-5.14 (1H, d), 5.13-5.08 (1H, d), 4.55-4.3 (3H, m), 4.25-4.15 (1H, m), 3.9 (1.5H, s), 3.78 (1.5H, s), 3.7-3.28 (3H, m), 2.45-2.32 (1H, m), 2.2-2.05 (1H, m).

Step C. **N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxyproline) methyl ester.** 4(R)-Allyloxyproline methyl ester hydrochloride (1.05 g, 4.75 mmol) and N-acetyl-Tyr-Val-OH (1.68 g, 5.21 mmol) were dissolved in 10 ml of a 1:1 mixture of dichloromethane and dimethylformamide and cooled to 0 °C. Diisopropylethylamine (1 ml, 5.93 mmol) was added to the cooled mixture followed by the addition of N-hydroxybenzotriazole (0.769 g, 5.69 mmol) and 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.18 g, 6.2 mmol). After stirring for 2 hours, the mixture was warmed to room temperature and stirred for 16 hours. The reaction was poured into 150 ml of ethyl acetate and washed with 50ml each of water, 10% sodium hydrogen sulfate, and 10% sodium bicarbonate. The organic layer was dried over sodium sulfate, filtered, and evaporated to give a light yellow solid. This was purified by flash chromatography eluting with dichloromethane/methanol/pyridine (100:3:0.5) to give 780 mg of the title compound. ¹H NMR (CD₃OD) δ 7.02-6.96 (2H, d), 6.67-6.63 (2H, d), 5.95-5.85 (1H, m),

- 231 -

5.34-5.27 (1H, d), 5.16-5.13 (1H, d), 4.53-4.38 (3H, m), 4.28-4.22 (1H, m), 4.12-3.97 (3H, m), 3.82-3.73 (1H, m), 3.72 (3H, s), 3.04-2.88 (2H, m), 2.85-2.72 (2H, m), 2.45-2.34 (1H, m), 2.08-1.95 (2H, m), 1.92 (3H, s), 1.00-0.92 (6H, 2 x d).

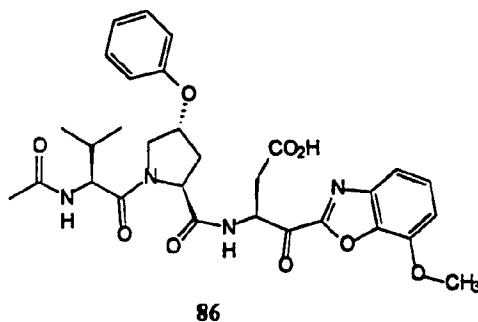
Step D. **N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxyprolinyl))-3(S)-amino-4-oxobutanoic acid tert-butyl ester semicarbazone.** N-Acetyl-tyrosinyl-valinyl-(4-allyloxyproline) methyl ester (770 mg, 1.57 mmol) was dissolved in 20 ml of tetrahydrofuran and 4 ml of methanol. Lithium hydroxide (145 mg, 3.46 mmol) was added to the mixture and stirred at room temperature. After two hours, 1 ml of 10% hydrogen chloride was added and the mixture evaporated in vacuo to give a solid residue then partitioned between 5ml of water and 50 ml of ethyl acetate and the organic layer separated and evaporated in vacuo to give 430 mg of the acid that was used immediately in the next step.

N-Acetyl-tyrosinyl-valinyl-4-allyloxyproline (420 mg, 0.88 mmol) and 3-amino-4-oxobutyric acid tert-butyl ester semicarbazone (184 mg, 0.8 mol, Graybill et al., Int. J. Protein Res., 44, pp. 173-82 (1994)) to give 100 mg (20%) of the title compound as a white amorphous solid: ^1H NMR (CD_3OD) δ 7.24-7.2 (1H, m), 7.04-6.97 (2H, d), 6.73-6.65 (2H, d), 5.98-5.86 (1H, m), 5.35-5.24 (1H, d), 5.17-5.12 (1H, m), 4.12-3.98 (2H, m), 3.72-3.67 (1H, m), 2.98-2.92 (3H, m), 2.38-2.32 (1H, m), 2.1-2.02 (2H, m), 1.92 (3H, s), 0.98-0.89 (6H, 2 x d).

- 232 -

Step E. N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxyprolinyl))-3(S)-amino-4-oxobutanoic acid (85). N-(N-Acetyl-tyrosinyl-valinyl-(4(R)-allyloxyprolinyl))-3(S)-amino-4-oxobutanoic acid tert-butyl ester semicarbazone (100 mg) was deprotected as described (Example 3, compound K, Step C) to give 44.2 mg (53%) of the title compound: ¹H NMR (CD₃OD) δ 7.04-6.97 (2H, d), 6.72-6.65 (2H, d), 5.97-5.86 (1H, m), 5.32-5.25 (1H, d), 5.17-5.12 (1H, d), 4.62-4.40 (3H, m), 4.30-4.13 (2H, m), 4.12-3.96 (3H, m), 3.75-3.68 (1H, m), 2.99-2.92 (1H, m), 2.78-2.70 (1H, m), 2.70-2.48 (2H, m), 2.35-2.30 (1H, m), 2.17-1.95 (2H, m), 1.92 (3H, s), 0.98-0.88 (6H, 2 x d).

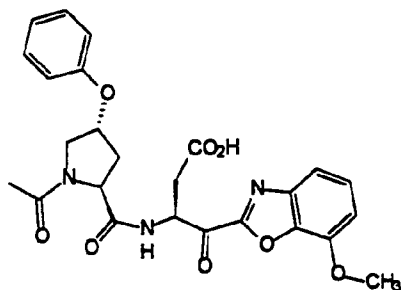
Compounds 86 and 87 were prepared by a similar method described for the synthesis of 69a in example 5:



N-Acetyl-(S)-valinyl-(4-(S)-phenoxy)prolinyl-3(S)-amino-4-(7-methoxybenzoxazol-2-yl)-4-oxo-butanoic acid (86). N-Acetyl-(S)-valinyl-(S)-(4-(S)-phenoxy)proline was converted to 86 as a white powder: ¹H NMR (DMSO-d₆) δ 8.75(d, 1H), 7.6-7.2(m, 4H), 7.0-6.8(m, 4H), 5.5(m, 1H), 5.05(s, 1H), 4.5(t,

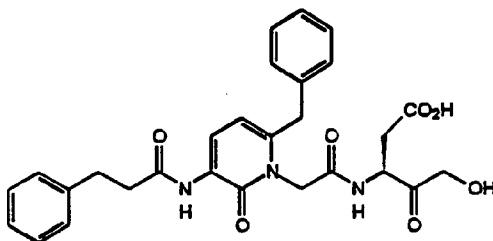
- 233 -

1H), 4.29(t, 1H), 4.0(s, 3H), 4.0-3.8(m, 2H), 3.0-2.8(dd, 2H), 2.3(m, 1H), 2.09(m, 1H), 1.95-1.8(m, 2H), 1.78(s, 3H), 1-0.7(dd, 6H).



87

5 **N-Acetyl(4-(R)-phenoxy)prolinyl-3(S)-amino-4-(7-methoxybenzoxazol-2-yl)-4-oxo-butanoic acid (87):** N-Acetyl-(S)-(4-(S)-phenoxy)proline was converted to 87 as a white powder: ¹H NMR (DMSO-d₆) δ 9.1(d, 1H), 8.76(d, 1H), 7.6-7.2(m, 4H), 7.0-6.9(m, 4H), 5.55(m, 1H), 5.45(m, 1H), 5.0(m, 2H), 4.56(t, 1H), 4.40(t, 1H), 4.0(s, 3H), 3.9(dd, 1H), 3.76(d, 1H), 3.64(d, 1H), 3.1-2.9(m, 1H), 2.8(m, 1H), 2.50(m, 1H), 2.3-2.2(m, 1H), 2.09(m, 1H), 1.95 and 1.75(2 x s, 3H, rotamers)



88

15 **N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl)acetyl-3(S)-amino-5-hydroxy-4-oxo-pentanoic acid (88).** N-2-(6-Benzyl-

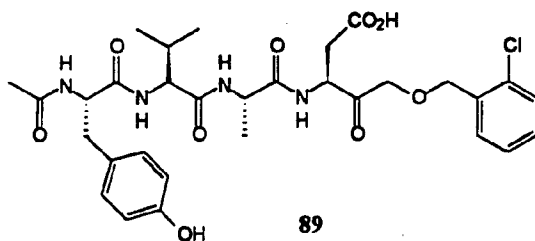
- 234 -

1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl) acetyl-3(S)-amino-5-hydroxy-4-oxo-pentanoic acid tert-butyl ester was prepared from **52b** and **81** following the method described for the synthesis of **83a** to give a white solid (45%): $^1\text{H NMR}(\text{CDCl}_3)$ δ 8.40(d, 1H), 8.20(s, 1H), 7.4-7.1(m, 11H), 6.18(s, 1H), 4.72(m, 1H), 4.65-4.5(q, 2H), 4.4-4.2(dd, 2H), 4.0(s, 2H), 3.04(t, 2H), 2.9(dd, 1H), 2.76(t, 2H), 2.55(dd, 1H), 1.39(s, 9H).

The resulting product was converted to **88** by method described in example 5, compound **84a** to give the title compound (42%) as a white solid: $^1\text{H NMR}(\text{CDCl}_3)$ δ 8.5(d, 1H), 8.1(d, 1H), 8.0(m, 1H), 7.4-7.1(m, 11H), 6.3(d, 1H), 4.9-4.8(m, 2H), 4.6-4.4(m, 2H), 4.3(dd, 1H), 4.1(s, 2H), 3.3(t, 1H), 3.05(t, 2H), 2.8-2.6(m, 3H)

Compounds **89** and **90** were prepared by a similar method described for the preparation of **84a** in example 5.

20

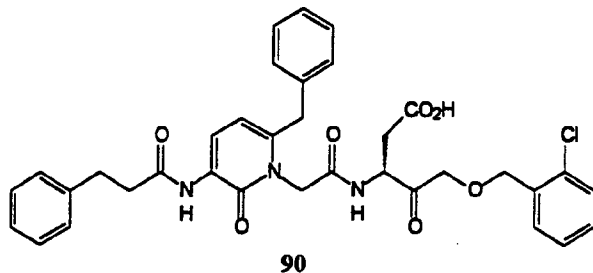
**89**

N-Acetyl-(S)-tyrosinyl-(S)-valinyl-(S)-alaninyl-3(S)-amino-5-(2-chlorobenzyloxy)-4-oxo-pentanoic acid (89) was prepared from Ac-Tyr-Val-Ala-OH and (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethoxyl)-4-oxo-pentanoate (prepared by a similar method as **82**) to give a white solid: $^1\text{H NMR}$ (DMSO-

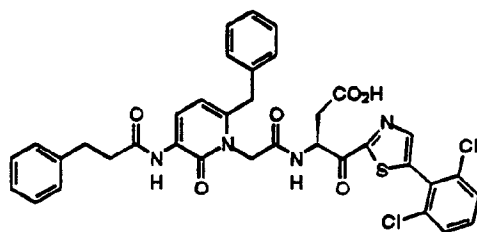
25

- 235 -

δ 9.15(s, 1H), 8.5(d, 1H), 7.98(d, 1H), 7.75(d, 1H), 7.55-7.3(m, 4H), 7.0(d, 1H), 6.6(d, 2H), 4.6-4.3(m, 6H), 4.3-4.1(m, 2H), 2.9(d, 1H), 2.76(dd, 1H), 2.7-2.5(m, 2H), 1.95(m, 1H), 1.75(s, 3H), 1.2(d, 3H), 0.9-0.7(dd, 6H)



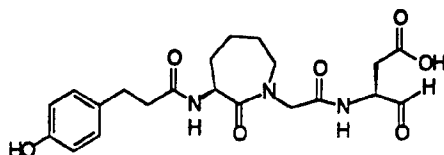
N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl) acetyl-3-amino-5-(2-chlorobenzyloxy)-4-oxo-pentanoic acid (90) was prepared from 52b and (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenyl-methoxyl)-4-oxo-pentanoate (prepared by a similar method as 82) to give a white solid: ^1H NMR(DMSO- d_6) δ 9.2(s, 1H), 8.75(d, 1H), 7.7-7.1(m, 14H), 6.4(d, 1H), 4.65(d, 6H), 4.56(s, 1H), 4.6-4.35(dd, 1H), 3.9(s, 2H), 2.9-2.6(m, 6H)



N-2-(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionyl)amino-1-pyridyl) acetyl-3(S)-amino-5-(5-(2,6-dichlorophenyl) thiazol-2-yl)-4-oxo-pentanoic

- 236 -

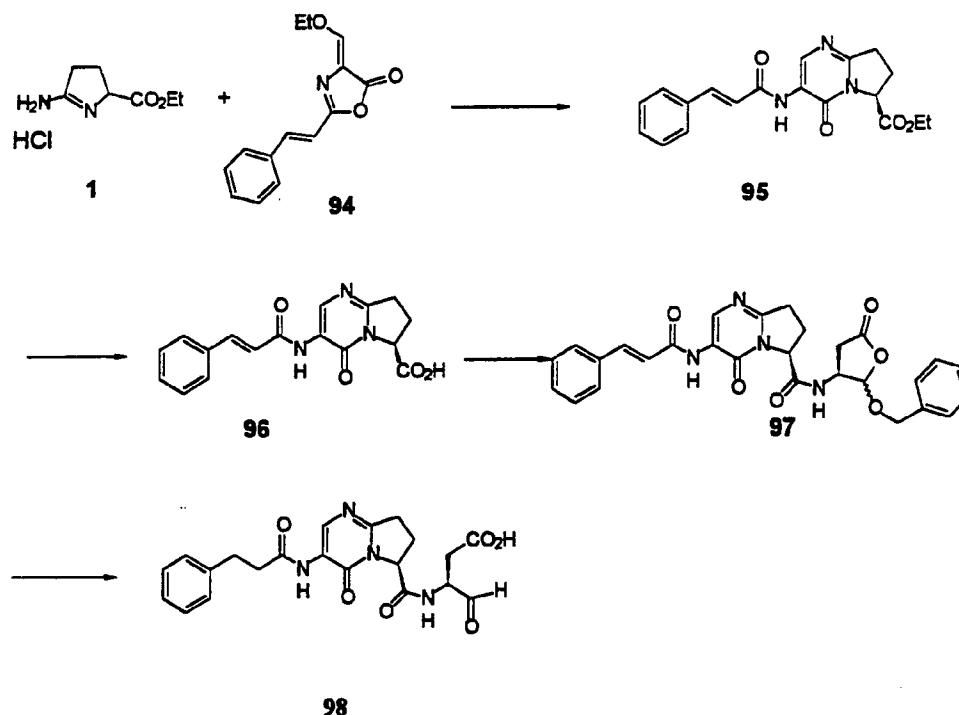
acid (91) was prepared from 52b and 3-(Allyloxycarbonyl)-amino-4-[(2,6-dichloro-phenyl)-thiazol-2-yl]-4-hydroxy-butyric acid tert-butyl ester (99) as described for the preparation of 69a to give an off-white powder: ^1H NMR(DMSO- d_6) δ 9.32(s, 1H), 9.05(d, 1H), 8.27(d, 1H), 8.18(d, 1H), 7.7(d, 1H), 7.6(t, 1H), 7.4-7.1(m 11H), 6.1(d, 1H), 5.64(m, 1H), 4.8-4.6(dd, 2H), 3.85(s, 2H), 3.02(m, 1H), 2.9-2.7(m, 4H).



92

3-(S)-(2-(3-(S)-(4-Hydroxy-phenyl)-propionylamino)-2-oxo-azepan-1-yl)-acetyl-amino-4-oxo-butyric acid (92) was prepared from 2-(3-(S)-(4-Hydroxy-phenyl)-propionylamino)-2-oxo-azepan-1-yl)-acetic acid and N-allyloxycarbonyl-4-amino-5-benzyloxy-2-oxotetrahydrofuran (Chapman, Biorg. Med. Chem. Lett., 2, pp. 613-18 (1992)) by a similar method described for the synthesis of 54a to give the title compound as a white solid: ^1H NMR(DMSO- d_6) δ 9.10-9.20(s, 1H), 8.40(s, 1H), 7.88(d, 1H), 7.0(d, 2H), 6.64(d, 2H), 4.60(t, 1H), 4.10(q, 2H), 3.9-4.2(m, 2H), 3.6(m, 1H), 3.18(d, 2H), 2.70(t, 2H), 2.40(m, 2H), 1.85-1.40(m, 8H).

- 237 -



4-Ethoxymethylene-2-styryl-4H-oxazol-5-one (94) was prepared according to Cornforth, The Chemistry of Penicillin, Clarke, Johnson, Robinson, (eds.)

5 Princeton University Press, p. 804 (1949)

4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydropyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid ethyl ester (95) was prepared from 94 by the procedure in example 5 for compound 3 to give 4.5g (30%) of the title compound: ^1H NMR (CD_3OD) δ 1.3 (t, 3H), 2.35 (m, 1H), 2.65 (m, 1H), 3.1 (m, 1H), 3.15 (m, 1H), 4.25 (q, 2H), 5.15 (dd, 1H), 6.95 (d, 1H), 7.4 (m, 3H), 7.6 (m, 2H), 7.65 (d, 1H), 8.95 (s, 1H).

10

- 238 -

4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid (96) A mixture of 4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid ethyl ester (95, 3.1g, 8.8mmol) and aqueous 1N lithium hydroxide (8.8mL, 8.8mmol) in methanol (10mL) was stirred 18h at room temperature. The reaction was diluted with water and washed with ethyl ether (1 x 20mL). The aqueous layer was acidified with conc. hydrochloric acid. The solid was collected by filtration and washed with water. The solid was dried in a vacuum oven at 50 °C for 18h to give 2.2g (75%) of the title compound as a tan solid: ¹H NMR(CD₃OD) δ 2.4(m, 1H), 2.7(m, 1H), 3.1(m, 1H), 3.2(m, 1H), 5.15(dd, 1H), 7.0(d, 1H), 7.4(m, 3H), 7.6(m, 2H), 7.65(d, 1H), 8.95(s, 1H)

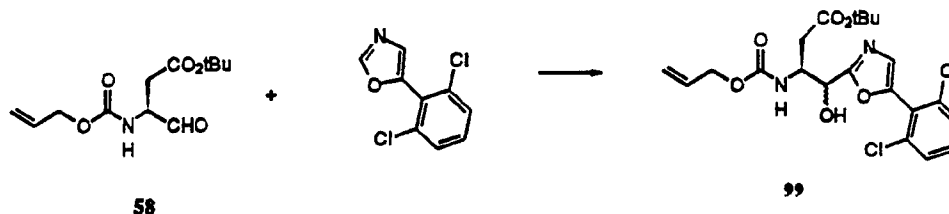
4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid (2-benzyloxy-5-oxo-tetrahydro-furan-(3S)-yl)-amide (97) was prepared from 96 by the method described in example 3 for compound H, step A to give 0.52g (75%) of the title compound as a mixture of diastereomers: ¹H NMR(CDCl₃) δ 2.3-2.7(m, 3H), 2.9(dd, 1H), 3.05(m, 1H), 3.3(m, 1H), 4.4-4.8(m, 2H), 4.9(2 x d, 1H), 5.05(m, 1H), 5.55(2 x s, 1H), 6.6(2 x d, 1H), 7.4(m, 6H), 7.55(m, 4H), 7.65(2 x d, 1H), 8.0(m, 2H), 9.2(s x 2, 1H).

4-Oxo-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyric acid (98) was prepared by the procedure in example 3 for compound H, step D to

- 239 -

give 0.13g (45%) of the title compound: ^1H

NMR(CD_3OD) δ 2.35(m, 1H), 2.45-2.75(m, 3H), 2.8(t, 2H), 3.0(t, 2H), 3.1(m, 1H), 3.25(m, 1H), 4.3(m, 1H), 6.65(dd, 1H), 5.15(m, 1H), 7.15(m, 1H), 7.3(m, 4H), 8.8(a, 1H).



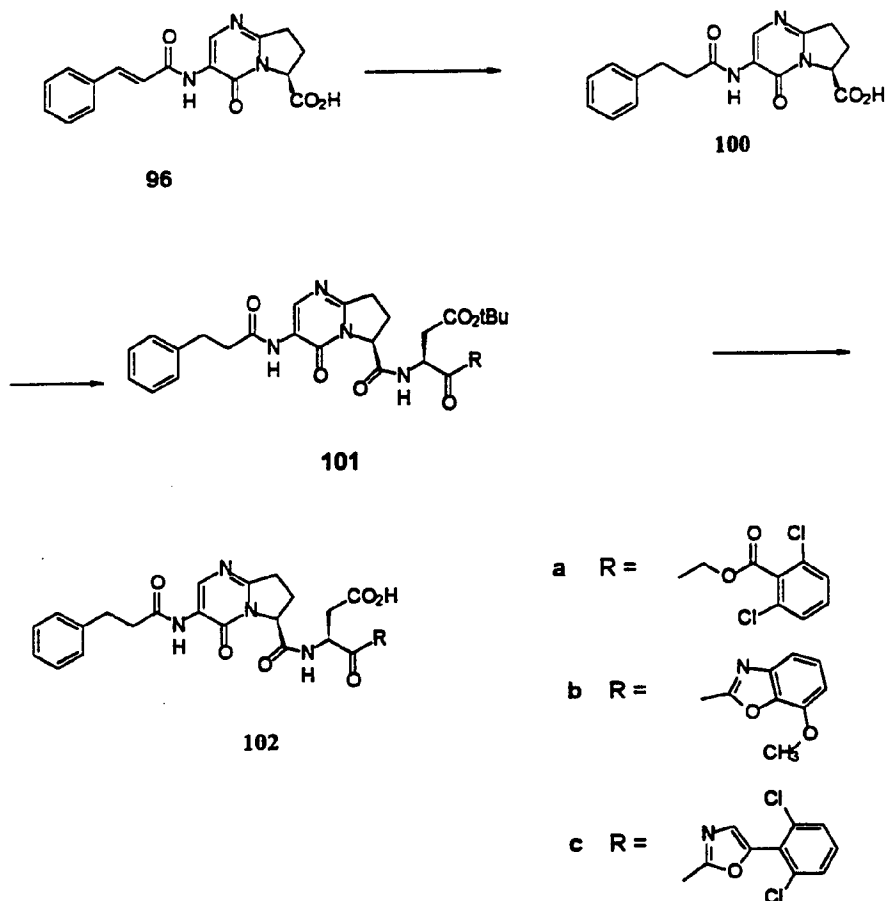
3(S)-((Allyloxycarbonyl)-amino-4-[(2,6-dichlorophenyl)-oxazol-2-yl]-4(R,S)-hydroxy-butyl) ester (99). A solution of 5-(2,6-Dichlorophenyl)oxazole (2.71g, 12.7mmol; prepared by a similar method described in Tet. Lett. 23, p2369 (1972)) in tetrahydrofuran (65mL) was cooled to -78 °C under a nitrogen atmosphere. To this solution was added n-butyl lithium (1.5M solution in hexanes, 8.5mL, 13.3mmol) and stirred at -78 °C for 30min. Magnesium bromide etherate (3.6g, 13.9mmol) was added and the solution was allowed to warm to -45 °C for 15min. The reaction was cooled to -78 °C and aldehyde 58 (3.26g, 12.7mmol; Graybill et al., Int. J. Protein Res., 44, pp. 173-182 (1993)) in tetrahydrofuran (65mL) was added dropwise. The reaction was stirred for 25min., then allowed to warm to -40 °C and stirred for 3h, and then at room temperature for 1h. The reaction was quenched with 5% NaHCO_3 (12mL) and stirred for 3h. The tetrahydrofuran was removed in vacuo and the resulting residue was extracted with dichloromethane. The organic layer was washed with saturated sodium chloride solution and dried over magnesium sulfate,

- 240 -

filtered, and concentrated to yield 6.14g of the title compound. Purification gave 4.79g (80%) of 99: ^1H NMR (CDCl_3) δ 1.45(s, 9H), 2.7-2.5(m, 2H), 2.8(dd, 1H), 4.2, 4.4(2 x d, 1H), 4.7-4.5(m, 3H), 5.35-5.1(m, 2H), 5.6, 5.7(2 x d, 1H), 6.0-5.8(m, 1H), 7.2(d, 1H), 7.3(m, 1H), 7.4(m, 2H).

4-Oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo [1,2-a]pyrimidine-(6S)-carboxylic acid (100).
A mixture of 4-Oxo-3-(3-phenyl-acryloylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carboxylic acid (96; 2.1g, 6.5mmol) and 20% palladium hydroxide on carbon (0.5g) in methanol (50mL) was stirred under a hydrogen atmosphere for 4h. The resulting mixture was filtered and concentrated to yield 2.1g (100%) of the title compound as a white solid: ^1H NMR(CD_3OD) δ 2.35(m, 1H), 2.65(m, 1H), 2.75(t, 2H), 3.0(t, 2H), 3.1(m, 1H), 3.15(m, 1H), 5.1(dd, 1H), 7.15(m, 1H), 7.25(m, 4H), 8.75(s, 1H)

- 241 -



2,6-Dichloro-benzoic acid 4-tert-butoxycarbonyl-2-oxo-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyl ester (101a) was prepared by the procedure in example 5 for compound 56a to give 0.16g (20%) of the title compound: $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ 1.45(s, 9H), 2.3(m, 1H), 2.6(m, 1H), 2.7(m, 3H), 2.95(m, 3H), 4.8(m, 1H), 5.1(m, 1H), 5.2(q, 2H), 7.1(m, 1H), 7.2(m, 4H), 7.4(m, 3H), 8.75(s, 1H).

4-(7-methoxy-benzoxazol-2-yl)-4-oxo-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butric

- 242 -

acid tert-butyl ester (101b). 4-Hydroxy-4-(7-methoxy-benzoxazol-2-yl)-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyric acid tert-butyl ester was prepared from 100 and 66a by the procedure in example 5 for compound 67a to give 0.95g (quantitative) of the product as a mixture of diastereomers: $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ 1.45(2 x s, 9H), 2.2(2 x m, 1H), 2.35-3.0(m, 9H), 4.0(m, 3H), 4.75(m, 1H), 4.85(m, 1H), 5.05(2 x dd, 1H), 7.1(2 x dd, 1H), 7.15-7.3(m, 4H), 7.5(2 x t, 1H), 7.8(2 x d, 1H), 8.55(2 x dd, 1H), 8.7(2 x s, 1H). The resulting product was converted to 101b by the procedure in example 5 for compound 68a to give 0.36g (50%) of the title compound: $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ 1.4(s, 9H), 2.35(m, 1H), 2.55(m, 1H), 2.75(t, 2H), 2.95(t, 2H), 3.00(m, 1H), 3.1(dd, 2H), 3.15(m, 1H), 5.15(dd, 1H), 5.65(t, 1H), 7.1(m, 2H), 7.2(m, 4H), 7.4(m, 2H), 8.7(s, 1H).

4-[5-(2,6-Dichloro-phenyl)-oxazol-2-yl]-4-oxo-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyric acid tert-butyl ester (101c). 4-[5-(2,6-Dichloro-phenyl)-oxazol-2-yl]-4-hydroxy-(3S)-{[4-oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyric acid tert-butyl ester from 100 and 99 using the method described in example 5, compound 67a to give 0.09g (60%) of the product as a mixture of diastereomers: $^1\text{H NMR}(\text{CD}_3\text{OD})$ δ 1.45(2 x s, 9H), 2.2(m, 1H), 2.5(m, 2H), 2.7(2 x dd, 1H), 2.75(t, 2H),

- 243 -

2.9-3.1(m, 4H), 4.7(m, 1H), 5.1(m, 2H), 7.1(m, 1H),
7.1-7.25(m, 4H), 7.4(t, 1H), 7.5(t, 1H), 8.55(d, 1H),
8.75(s, 1H).

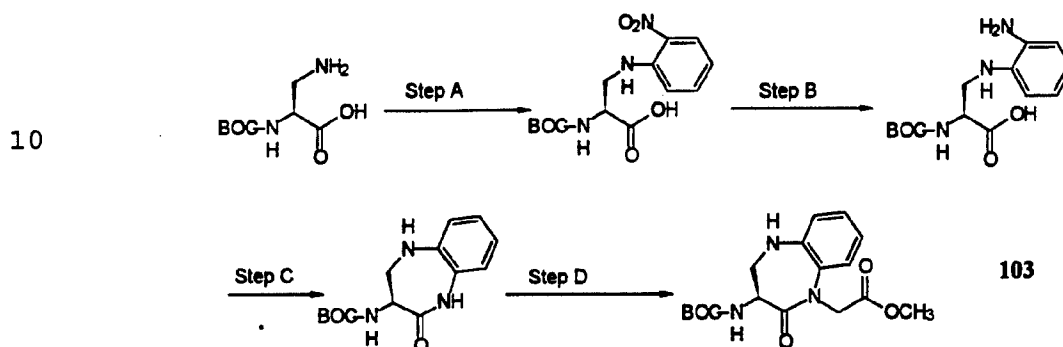
The resulting product was converted to 101c by the
method described in example 5, compound 68a to give
0.04g (45%) of the title compound: ¹H NMR(CD₃OD) δ
1.4(s, 9H), 2.3(m, 1H), 2.6(m, 1H), 2.75(t, 2H),
2.95(t, 2H), 2.9-3.2(m, 4H), 5.2(dd, 1H), 5.55(t,
1H), 7.1(m, 1H), 7.25(m, 4H), 7.55(m, 3H), 8.75(s,
1H).

2,6-Dichloro-benzoic acid 4-carboxy-2-oxo-(3S)-{[4-
oxo-3-(3-phenyl-propionylamino)-4,6,7,8-tetrahydro-
pyrrolo[1,2-a]pyrimidine-(6S)-carbonyl]-amino}-butyl
ester (102a) was prepared from 101a by the procedure
in example 5 for compound 57a to give 0.12g (80%) of
the title compound: ¹H NMR(CD₃OD) δ 2.35(m, 1H),
2.65(m, 1H), 2.75(m, 2H), 2.85(dd, 1H), 2.95(m, 2H),
3.0(dd, 1H), 3.15(m, 1H), 3.25(m, 1H), 4.55(dd, 1H),
5.15(m, 1H), 5.25(q, 2H), 7.15(m, 1H), 7.25(m, 4H),
7.45(m, 1H), 8.8(s, 1H).

4-(7-methoxy-benzoxazol-2-yl)-4-oxo-(3S)-{[4-oxo-3-(3-
phenyl-propionylamino)-4,6,7,8-tetrahydro-pyrrolo [1,2-
a]pyrimidine-(6S)-carbonyl]-amino}-butric acid (102b) was
prepared from 101b by the procedure described in example 5
for compound 69a to give 0.12g (35%) of the title
compound: ¹H NMR(DMSO-d₆) δ 2.1(m, 1H), 2.55(m, 1H), 2.7-
3.1(m, 8H), 4.05(s, 3H), 5.1(dd, 1H), 5.55(t, 1H), 7.2(m,
1H), 7.25(m, 5H), 7.5(t, 1H), 7.55(d, 1H), 8.7(s, 1H),
9.2(d, 1H), 9.4(s, 1H), 12.7(br, 1H).

- 244 -

4- [5- (2,6-Dichloro-phenyl)-oxazol-2-yl]-4-oxo-(3S)-
 { [4-oxo-3 - (3-phenyl-propionylamino)-4,6,7,8-
 tetrahydro-pyrrolo[1,2-a] pyrimidine-(6S)-carbonyl]-
 amino}-butyric acid (102c) was prepared from 101c as
 5 described in example 5 for compound 69a to give 0.01g
 (40%) of the title compound: ^1H NMR (CD_3OD) δ 2.35 (m,
 1H), 2.6 (m, 1H), 2.75 (t, 2H), 2.95 (t, 2H), 3.05 (m,
 1H), 3.15 (m, 3H), 5.15 (dd, 1H), 5.55 (t, 1H), 7.15 (m,
 1H), 7.2 (m, 4H), 7.55 (m, 3H), 8.8 (s, 1H)



(3-tert-Butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-
 benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester
 (103).

Step A. 2(S)-tert-Butoxycarbonylamino-3-(2-
 15 nitrophenyl-amino)-propionic acid. 2-tert-
 Butoxycarbonylamino-3-aminopropionic acid (10 g, 49
 mmol), 2-fluoronitrobenzene (5.7 ml, 54 mmol), and
 sodium bicarbonate (8.25 g, 98 mmol) was taken into
 130 ml of dimethylformamide and heated at 80 °C for
 20 18 hours. The reaction was evaporated in vacuo to
 give a viscous orange residue that was dissolved in
 300 ml of water and extracted with diethyl ether (3 x
 150 ml). The aqueous solution was acidified to pH 5
 with 10 % sodium hydrogen sulfate and extracted with

- 245 -

ethyl acetate (3 x 250 ml). The combined extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to give 12.64 g (83 %) of the title compound as an orange amorphous solid. ¹H NMR (CD₃OD)

5 δ 8.15-8.10 (1H,d), 7.54-7.48 (1H,t), 7.13-7.08 (1H, d), 6.73-6.65 (1H, t), 4.45-4.35 (1H, m), 3.9-3.8 (1H, dd), 3.65-3.55 (1H, dd), 1.45 (9H, s).

Step B. 2(S)-tert-Butoxycarbonylamino-3-(2-aminophenyl-amino)-propionic acid. A mixture of 2-

10 tert-Butoxycarbonylamino-3-(2-nitrophenylamino)propionic acid (12.65 g, 40.5 mmol) and 0.5 g of 10% Pd/C in 100 ml of methanol under hydrogen at 1 atmosphere was stirred for 4 hrs. The solution was filtered through Celite 545 and the

15 filtrate evaporated in vacuo to afford 11.95 g of the title compound in quantitative yield as a dark brown solid that was used without purification. ¹H NMR (CD₃OD) δ 6.75-6.70 (3H,m), 6.65-6.58 (1H, m), 4.35-4.3 1H, m), 3.6-3.38 (2H, m), 1.45 (9H, s).

20 **Step C. 3(S)-tert-Butoxycarbonylamino-1,3,4,5-tetrahydro-benzo[b][1,4] diazepin-2-one.** 1-(3-Dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (8.54 g, 44.5 mmol) was added to a cooled (0 °C) solution of 2-tert-butoxycarbonylamino-3-(2-

25 aminophenylamino)propionic acid (11.95 g, 40.5 mmol) in 100 ml of dimethylformamide and stirred for 18 hours. The reaction was poured into 700 ml of ethyl acetate and washed four times with 100 ml of water. The organic layer was dried over anhydrous sodium

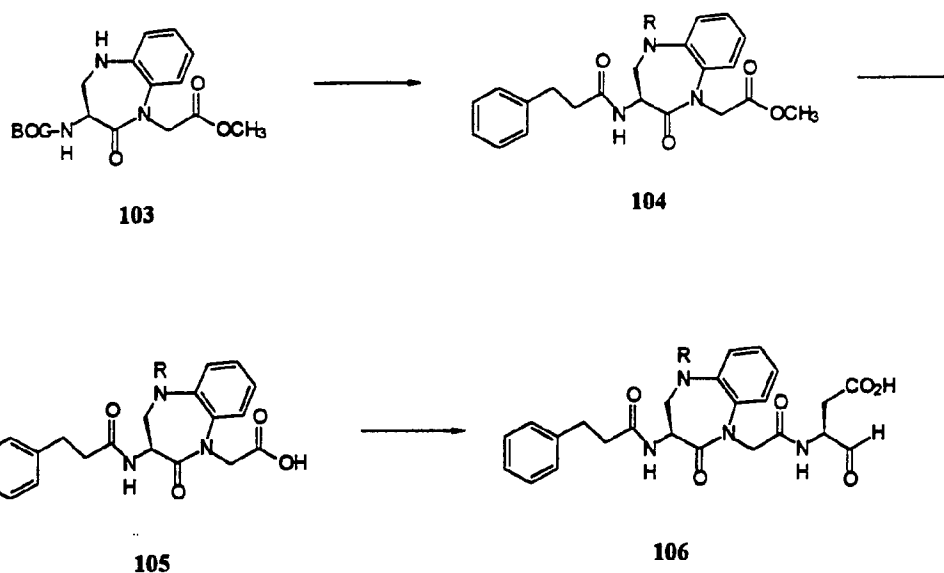
30 sulfate, filtered, and evaporated to give a brown solid that was purified by flash chromatography

- 246 -

eluting with 3:7 ethyl acetate/hexane to give 8 g
(71%) of the title compound: ^1H NMR (CDCl_3) δ 7.78 (1H, s), 7.02-6.95 (1H, m), 6.88-6.82 (1H, m), 6.82-6.78 (1H, m), 6.75-6.70 (1H, m), 5.8-5.7 (1H, d), 4.55-4.45 (1H, m), 3.95 (1H, s), 3.9-3.82 (1H, m), 3.48-3.40 (1H, m), 1.45 (9H, s).

Step D. (3(S)-tert-Butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (103). A 1.0 M solution of lithium bis(trimethylsilyl)amide (3.4 ml, 3.4 mmol) in THF was added dropwise to a -78°C solution of 3-tert-butoxycarbonylamino-1,3,4,5-tetrahydrobenzo[b][1,4]diazepin-2-one (0.94 g, 3.38 mmol) in 20 ml of anhydrous tetrahydrofuran and stirred for 30 minutes. Methyl bromoacetate (0.44 ml, 4 mmol) was added dropwise to the reaction mixture then warmed to room temperature. The reaction was diluted with 100 ml of ethyl acetate and washed with 0.3N potassium hydrogen sulfate (50 ml), water (2 x 50 ml), and brine. The combined organics were dried over anhydrous sodium sulfate, filtered, and evaporated to afford a gum that was purified by flash chromatography eluting with 3:7 EtOAc/Hex. to give 0.98 g (83%) of the title compound as a white solid. ^1H NMR (CDCl_3) δ 7.15-7.07 (2H, m), 6.98-6.94 (1H, m), 6.88-6.84 (1H, d), 5.62-5.55 (1H, d), 4.71-4.65 (1H, d), 4.65-4.6 (1H, m), 4.33-4.27 (1H, d), 3.96-3.90 (1H, m), 3.78 (3H, s), 3.44-3.37 (1H, m), 1.4 (9H, s).

- 247 -



a R = H

b R = COCH₂CH₂Phc R = CH₂Ph

- 5 **[2-Oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104a).** Anhydrous hydrogen chloride was bubbled into a solution of (3(S)-tert-butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (**103**, 1g, 2.86 mmol) in 25 ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid.
- 10 15 The hydrochloride salt and hydrocinnamic acid (0.47 g, 3.15 mmol) was dissolved into 20 ml of dimethylformamide and cooled to 0 °C. Diisopropylethylamine (1 ml, 5.72 mmol) was added to the solution followed by the addition of N-hydroxybenzotriazole and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After stirring for
- 20

- 248 -

18 hours at room temperature, the mixture was diluted with 150 ml of ethyl acetate and washed with 10% sodium hydrogen sulfate, 10% sodium bicarbonate, and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to a crude solid that was purified by flash chromatography eluting with 7:3 ethyl acetate/dichloromethane to afford 600 mg (55%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.3-6.85 (9H, m), 6.55-6.0 (1H, d), 4.88-4.82 (1H, m), 4.72-4.65 (1H, d), 4.28-4.22 (1H, m), 3.95-3.9 (1H, m), 3.78 (3H, s), 3.65 (1H, br. s), 3.28-3.2 (1H, m), 2.95-2.84 (2H, m), 2.55-2.4 (2H, m).

(3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid (105a). (3(S)-(3-Phenylpropionylamino)-2-oxo-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (104a) was dissolved in 90% methanol. Lithium hydroxide hydrate was added to the reaction and the reaction was stirred at room temperature for 4 h. The reaction was evaporated in vacuo to give a white solid. This was dissolved in 20 ml of water and acidified to pH 5 and extracted with ethyl acetate to afford 304 mg (88%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.5-6.9 (11H, m), 4.92-4.8 (1H, m), 4.7-4.58 (1H, d), 4.38-4.25 (1H, d), 3.88-3.78 (1H, m), 3.45-3.25 (1H, m), 3.05-2.85 (2H, m), 2.55-2.45 (2H, m).

4-Oxo-3(S)-{2-[2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro-benzo[b][1,4]diazepin-1-ylacetylaminobutyl]butyric acid (106a). N-[1-(2-Benzyloxy-

- 249 -

5-oxotetrahydrofuran-3-ylcarbamoyl-methyl)-2-oxo-2,3,4,5-tetrahydro-1H-benzo[b][1,4]diazepin-3-yl]-3-phenylpropionamide was prepared from 105a by the procedure in example 3, compound H (stepA) to afford 390 mg (93%) of the product as diastereomers. ¹H NMR (CD₃OD) δ 7.58-7.22 (14H, m), 5.78-5.73 (0.5 H, d), 5.64 (0.5 H, s), 5.0-4.72 (4H, m), 4.54-4.42 (2H, m), 3.82-3.76 (0.5 H, m), 3.68-3.62 (0.5 H, m), 3.28-3.21 (0.5H, m), 3.19-3.12 (0.5H, m), 3.07-2.98 (2H, m), 2.78-2.48 (4H, m).

The resulting product was converted to 106a by the method described in example 3, compound H (StepD) to afford the title compound as a white solid (17%): ¹H NMR (CD₃OD) δ 7.54-6.98 (9H, m), 5.58-5.44 (1H, m), 4.8-4.2 (4H, m), 3.96-3.3 (2H, m), 3.30-3.05 (1H, m), 2.98-2.25 (5H, m).

[2-Oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104b). Anhydrous hydrogen chloride was bubbled into a solution of (3(S)-tert-butoxycarbonylamino-2-oxo-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl)acetic acid methyl ester (103, 1g, 2.86mmol) in 25 ml of ethyl acetate for 2 minutes then stirred for 1 hour at room temperature. The reaction was evaporated to give 2-oxo-3(S)-amino-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl acetic acid methyl ester hydrochloride as a white solid. The hydrochloride salt was suspended into 20 ml of dichloromethane and cooled to 0 °C. Triethylamine (1.6 ml, 11.5 mmol) was added to the suspension followed by the dropwise addition of dihydrocinnamoyl

- 250 -

chloride (0.9 ml, 6 mmol). The mixture was warmed to room temperature and stirred for 18 hours. The mixture was diluted with 25 ml of dichloromethane and washed twice with 50 ml of water and once with 50 ml of brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with 1:1 ethyl acetate/dichloromethane to afford 1.35 g (92%) of the title product as a white solid. ¹H NMR (CDCl₃) δ 7.45-7.02 (14 H, m), 6.37-6.32 (1H, d), 4.78-4.72 (1H, m), 4.52-4.3 (3H, m), 3.82-3.77 (1H, m), 3.74 (3H, s), 3.03-2.87 (4H, m), 2.58-2.45 (2H, m), 2.45-2.35 (1H, m), 2.25-2.16 (1H, m).

[2-Oxo-5-(3-phenylpropionyl)-3-(3(S)-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid (105b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (**104b**; 680 mg, 1.32 mmol) was hydrolyzed by the procedure in example 105a to afford 645 mg (98%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.58 (1H, br. s), 7.5-7.42 (1H, m), 7.35-6.95 (14H, m), 4.95-4.88 (1H, m), 4.64-4.55 (1H, d), 4.54-4.45 (1H, t), 4.15-4.05 (1H, d), 3.75 (1H, m), 3.05-2.75 (4H, m), 2.58-2.45 (2H, m), 2.45-2.28 (1H, m), 2.25-2.14 (1H, m).

2-Oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenyl-propionyl-amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]

- 251 -

acetylamino}butyric acid (106b). [2-Oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid and 3-amino-4-oxobutyric acid tert-butylester

5 semicarbazone were coupled by the procedure in example 3, compound K (step A) to give 350 mg (85%) of a white solid. ¹H NMR (CDCl₃) δ 9.05 (1H, br. s), 7.58-7.55 (1H, d), 7.5-7.35 (1H, m), 7.35-6.95 (14 H, m), 6.75-6.72 (1H, d), 6.25 (1H, br. s), 5.25 (1H, br. s),

10 4.95-4.88 (1H, m), 4.8-4.72 (1H, m), 4.55-4.4 (2H, m), 3.92-3.88 (1H, d), 3.73-3.68 (1H, m), 2.95-2.8 (4H, m), 2.8-2.72 (1H, m), 2.62-2.55 (1H, m), 2.55-2.45 (2H, m), 2.4-2.32 (1H, m), 2.2-2.12 (1H, m), 1.45 (9H, s).

15 4-Oxo-3-{2-[2-oxo-5-(3-phenylpropionyl)-3-(3-phenylpropionyl -amino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetyl-amino}butyric acid tert-butyl ester semicarbazone was deprotected as described in example 3, compound K

20 (step C) to give 118 mg (47%) of the title compound as a white solid. ¹H NMR (CD₃OD) δ 7.48-6.95 (14 H, m), 4.65-4.15 (6H, m), 3.5-3.4 (1H, m), 2.85-2.72 (4H, m), 2.65-2.5 (1H, m), 2.5-2.34 (3H, m), 2.34-2.15 (2H, m).

25 [5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro -benzo[b][1,4]diazepin-1-yl]acetic acid methyl ester (104c). [2-Oxo-3-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo-

30 [b][1,4]diazepin-1-yl]acetic acid methyl ester (104a; 500 mg, 1.31 mmol), calcium carbonate (155 mg, 1.58 mmol), and benzyl bromide (170 μl, 1.44 mmol) were taken into 10 ml of dimethylformamide and heated to 80 °C for 8 hours. The mixture was diluted with 150 ml

- 252 -

of ethyl acetate and washed 4 times with 50 ml of water. The organic layer was dried over anhydrous sodium sulfate, filtered, and evaporated to give a viscous, yellow oil that was purified by flash chromatography eluting with dichloromethane/ethyl acetate (8:2) to give 460 mg (75%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.34-7.05 (14 H, m), 6.32-6.28 (1H, d), 4.84-4.76 (1H, d), 4.76-4.70 (1H, m), 4.43-4.37 (1H, d), 4.26-4.18 (1H, d), 4.06-4.00 (1H, d), 3.79 (3H, s), 3.45-3.37 (1H, m), 3.02-2.95 (1H, m), 2.90-2.82 (2H, m), 2.5-2.34 (2H, m).

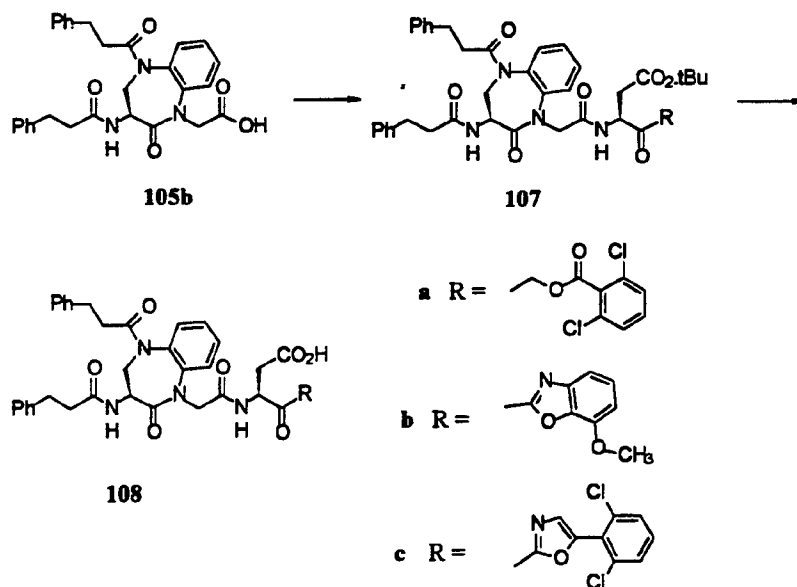
[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro -benzo[b][1,4]diazepin-1-yl]acetic acid (105c) was prepared by the hydrolysis of the ester (102c) by the procedure reported in example 105a to give 450 mg (98%) of the title compound as a white solid: ¹H NMR (CD₃OD) δ 7.5-7.05 (14 H, m), 6.4 (1H, br. s), 4.85-4.55 (2H, m), 4.5-4.21 (2H, m), 4.12-3.92 (1H, d), 3.45-3.3 (1H, m), 3.1-2.8 (3H, m), 2.55-2.28 (3H, m).

3(S)-{2-[5-Benzyl-2-oxo-3-(3(S)-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino}-4-oxobutyric acid (106c). [5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetic acid and 3(S)-amino-4-oxobutyric acid tert-butylester semicarbazone were coupled by the procedure in example 3, compound K (step A) and to afford 260 mg (85%) of a white solid: ¹H NMR (CD₃OD) δ 7.35-7.0 (15 H, m), 4.94-4.88 (1H, m), 4.68-4.58 (1H, d), 4.57-4.52 (1H, m), 4.41-4.34

- 253 -

(1H, d), 4.3-4.23 (1H, d), 4.1-4.04 (1H, d), 3.18-3.11 (1H, m), 3.09-2.98 (1H, m), 2.78-2.72 (2H, t), 2.65-2.57 (1H, m), 2.42-2.33 (3H, m).

3(S)-{2-[5-Benzyl-2-oxo-3(S)-(3-phenylpropionylamino)-
 5 2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-
 acetyl-amino}-4-oxobutyrlic acid tert-butyl ester
 semicarbazone was deprotected as described in example
 3, compound K (step C) to give 168 mg (81%) of the
 title compound as a white solid. ¹H NMR (CD₃OD) δ
 10 7.37-7.0 (14H, m), 4.75-4.62 (1H, m), 4.6-4.45 (2H,
 m), 4.4-4.21 (2H, m), 4.15-3.95 (2H, m), 3.15-3.0 (2H,
 m), 2.82-2.67 (2H, m), 2.65-2.52 (1H, m), 2.5-2.32
 (3H, m).



2,6-Dichlorobenzoic acid 4-tert-butoxycarbonyl-2-oxo-
 15 3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-
 phenylpropionylamino)-2,3,4,5-tetrahydro-
 benzo[b][1,4]diazepin-1-yl]acetyl-amino}butyl ester
 (107a). The resulting semicarbazone was prepared by
 the coupling of compound 105b and t-butyl 3-

- 254 -

(allyloxycarbonylamino)-4-oxo-5-(2,6-dichlorobenzoyloxy)pentanoate (WO 93 16710) as described in compound 56a to give 256 mg (58%) of the title compound as a white solid. ¹H NMR (CDCl₃) δ 7.45-7.04 (17H, m), 6.45-6.34 (2H, m), 5.28-5.21 (1H, m), 5.1-5.0 (1H, m), 4.95-4.90 (1H, m), 4.75-4.70 (1H, m), 4.55-4.44 (1H, m), 4.32-4.22 (1H, dd), 3.99-3.85 (1H, dd), 3.85-3.76 (1H, m), 3.06-2.83 (5H, m), 2.83-2.74 (1H, m), 2.6-2.44 (2H, m), 2.43-2.33 (1H, m), 2.24-2.15 (1H, m), 1.45 (9H, s).

2,6-Dichlorobenzoic acid 4-carboxy-2-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]acetylamino}butyl ester (108a) was prepared from 107a by the method described for compound 57a which afforded 156 mg (68%) of the title compound as a white solid. ¹H NMR (CD₃OD) δ 7.5-6.9 (17H, m), 5.16-5.02 (1H, dd), 4.88-4.71 (2H, m), 4.62-4.44 (2H, m), 4.42-4.28 (2H, m), 4.27-4.18 (1H, m), 3.47-3.41 (1H, m), 2.90-2.60 (5H, m), 2.46-2.4 (2H, m), 2.39-2.18 (2H, m).

4-(7-Methoxybenzoxazol-2-yl)-4-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid tert-butyl ester (107b). 4(R,S)-Hydroxy-4-(7-methoxybenzoxazol-2-yl)-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydro[b][1,4]diazepin-1-yl-acetylamino} butyric acid tert-butyl ester was prepared from 105b and 66a by the method described in example 5, compound 67 to

- 255 -

give 56% of a white solid: ^1H NMR (CDCl_3) δ 7.72-6.78 (19H, m), 6.37-6.28 (1H, m), 5.17-5.08 (0.5H, m), 4.92-4.82 (0.5H, m), 4.81-4.6 (1H, m), 4.6-4.35 ((3H,m), 4.05-3.9 (1H, m), 3.95 (3H, s), 3.82-3.7 (1H, m), 2.96-2.05 (10H, m), 1.45 (4.5H, s), 1.38 (4.5H, s).

The resulting product was converted to 107b by the method described in example 5, compound 68a to give the title compound (56%) as a white solid. ^1H NMR

(CD_3OD) δ 7.62-6.8 (17H, m), 5.64-5.58 (0.5H, t), 5.52-5.46 (0.5H, t), 4.62-4.47 (2H, m), 4.40-4.32 (1H, m), 3.9 (1.5H, s), 3.88 (1.5 H, s), 3.43-3.37 (1H, m), 3.0-2.92 (1H, m), 2.90-2.62 (6H, m), 2.5-2.4 (2H, m), 2.28-2.15 (2H, m), 1.32 (4.5H, s), 1.25 (4.5H, s).

4-(7-Methoxybenzoxazol-2-yl)-4-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid (108b) was prepared by the method described in example 5, compound 69a to give the title compound (50%) as a white solid. ^1H NMR (CD_3OD) δ 7.41-6.88 (17H, m), 5.6-5.55 (0.5H, t), 5.48-5.43 (0.5H, t), 4.64-4.45 (2H, m), 4.45-4.30 (1H, m), 3.93 (1.5H, s), 3.90 (1.5H, s), 3.47-3.34 (1H, m), 3.10-2.85 (2H, m), 2.84-2.63 (5H, m), 2.6-2.4 (2H, m), 2.3-2.1 (2H, m).

4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-4-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid tert-butyl ester (107c). 4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-4(R,S)-hydroxy-3(S)-{2-[2-

- 256 -

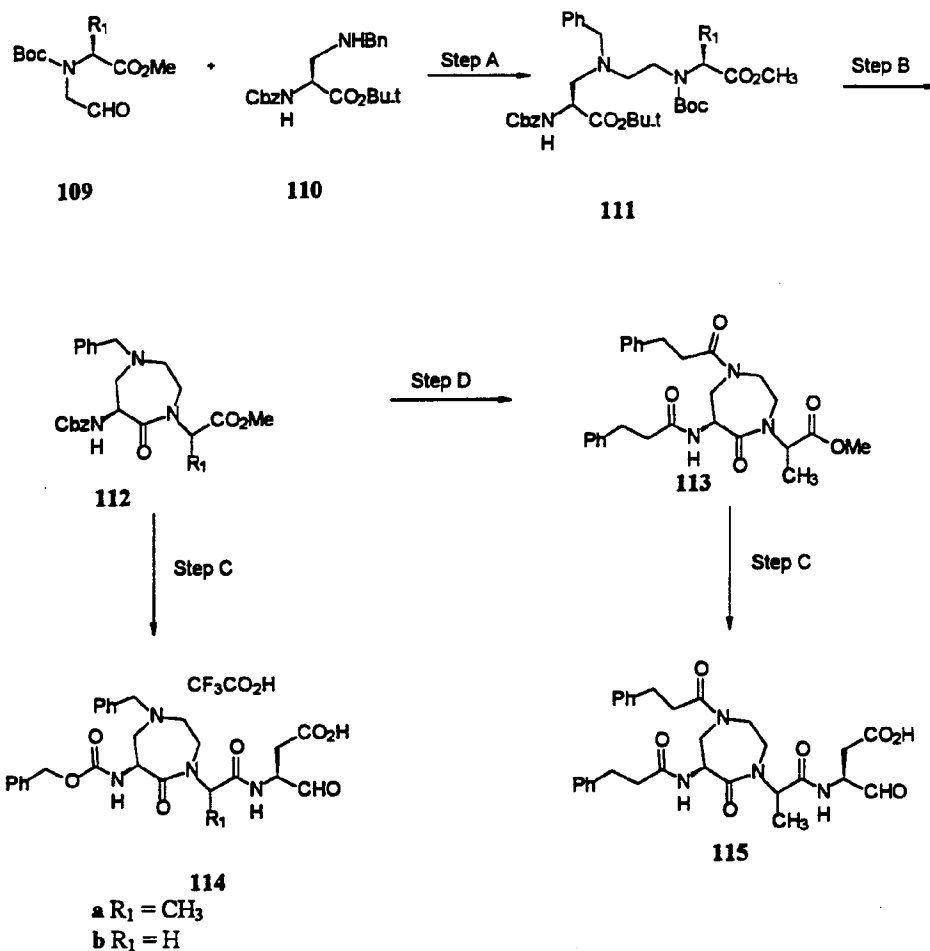
oxo- 5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid tert-butyl ester was prepared from 106c and 99 by a similar method as described for compound 67a in example 5 to give 72% of a white solid. ¹H NMR (CDCl₃) δ 7.71-7.64 (1H, m), 7.58-7.42 (2H, m), 7.42-6.92 (15H, m), 6.5-6.37 (2H, m), 5.15-5.04 (1H, m), 4.88-4.68 (2H, m), 4.57-4.37 (2H, m), 4.28-4.13 (1H, m), 3.87-3.64 (2H, m), 3.04-2.80 (4H, m), 2.76-2.68 (1H, m), 2.67-2.42 (3H, m), 2.41-2.31 (1H, m), 2.22-2.12 (1H, m), 1.45 (9H, s).

The resulting product was converted to 107c by a similar method as described for compound 68a in example 5 to give the title compound in quantitative yield as a white solid. ¹H NMR (CDCl₃) δ 7.47-6.98 (18H, m), 6.52-6.42 (1H, d), 5.6-5.52 (1H, m), 4.78-4.71 (1H, m), 4.52-4.40 (2H, m), 4.03-3.94 (0.67H, m), 3.94-3.85 (0.33H, m), 3.85-3.75 (1H, m), 3.45-3.33 (1H, m), 3.08-2.98 (1H, m), 2.97-2.84 (4H, m), 2.55-2.43 (2H, m), 2.43-2.32 (1H, m), 2.23-2.13 (1H, m), 1.35 (9H, s).

4-[5-(2,6-Dichlorophenyl)oxazol-2-yl]-4-oxo-3(S)-{2-[2-oxo-5-(3-phenylpropionyl)-3(S)-(3-phenylpropionylamino)-2,3,4,5-tetrahydrobenzo[b][1,4]diazepin-1-yl]-acetylamino} butyric acid (108c) was prepared from 107c by a similar method as described for compound 69a in example 5 to give 72% the title compound as a white solid. ¹H NMR (CD₃OD) δ 7.58-7.0 (18H, m), 5.62-5.53 (0.67H, m), 5.52-5.47 (0.33H, m), 4.68 (3H, m), 3.54-3.42 (1H, m), 3.1-2.92 (2H, m), 2.88-2.68 (5H, m),

- 257 -

2.63-2.45 (2H, m) 2.40-2.22 (2H, m).



3 (S) - {2 (R,S) - [4-Benzyl-7-oxo-6 (S) - (N-benzoyloxycarbonylamino) - [1,4]diazepan-1-yl] - propionylamino} - 4-oxo-butyric acid trifluoroacetic acid salt (114a):

Step A. To a solution of tert-butyl-2-N-benzoyloxycarbonyl-3-N-benzyl-(S)-2,3-diaminopropionate (110; 0.85 g, 2.2 mmol), 3-(N-tert-butoxycarbonyl)amino-2-methyl-5-oxo-pentanoic acid methyl ester (109a; 0.65 g, 2.7 mmol), acetic acid (0.1 mL, 1.8 mmol), sodium acetate (0.36 g, 2

- 258 -

mmol) and 4 Å molecular sieves (1 g) in methanol (45 mL), was added sodium cyanoborohydride (0.33 g, 5.3 mmol). The mixture was stirred overnight at 25 °C then filtered through Celite and concentrated under reduced pressure. The residue was dissolved in 1 N NaOH and extracted with ethyl acetate (3 x 40 mL). The organic layer was dried (MgSO₄), filtered and evaporated to give an oil. Chromatography (silica-gel, 4:1 hexane: ethyl acetate as eluent) gave 0.92 g (68% yield) of 111a as an oil.

Step B. The above material was dissolved in dichloromethane (3 mL) cooled to 0 °C and treated with a 25% solution of trifluoroacetic acid in dichloromethane (20 mL) then allowed to warm to 25 °C and stir until the reaction was judged complete by TLC (4:1 hexane: ethyl acetate). The solvent was removed under reduced pressure and the residue dried under vacuum then dissolved in dichloromethane (40 mL) and treated with 4-methylmorpholine (1 mL, 9 mmol), HOBT (0.2g, 1.5 mmol) and EDC (0.61 g, 3.2 mmol). The resulting mixture was stirred overnight at 25 °C then diluted with dichloromethane and washed with water. The organic layer was dried (MgSO₄), filtered and evaporated to give an oil. Chromatography (silica-gel, 3:2 hexane: ethyl acetate) gave 0.49 g (74% yield) of 112a as a viscous oil.

Step C. A solution of 2(R,S)-[4-benzyl-7-oxo-6(S)-(N-benzyloxycarbonylamino)-[1,4]diazepan-1-yl]-propionic acid methyl ester (112a; 0.15 g, 0.32 mmol) was dissolved in methanol and treated with 1 M LiOH (0.32 mL) and stirred 5.5 hours at 25 °C then evaporated to dryness. The residue was azeotroped with ethanol (2 x 10 mL), acetonitrile (2 x 10 mL),

- 259 -

benzene (2 x 10 mL) then dried under vacuum. The resulting residue was converted to 114a by a method similar to that described in example 3, compound K (steps A, B, and C) and purified by reverse phase (C18 column) HPLC using 0.1%TFA:water/
5 0.1%TFA:acetonitrile as eluent. to give 17 mg (10% yield) of a viscous oil: ¹H NMR (500 MHz, CD₃OD) δ 1.15 (m, 3 H), 2.30- 2.70 (m, 6 H), 2.72- 2.95 (bm, 6 H), 3.30- 3.80 (m, 4 H), 4.10 (m, 1 H), 4.40 (m, 4
10 H), 4.95 (m, 1H) 6.95- 7.10 (bs, 5 H), and 7.12- 7.20 ppm (bs, 5 H).

3(S)-{2-[4-Benzyl-7-oxo-6(S)-(N-benzyloxycarbonylamino)-[1,4]diazepan-1-yl]-acetylamino}-4-oxo-butyric acid trifluoroacetic acid salt (114b) was prepared from 109b by a similar method described for the synthesis of 114a to give 85 mg of viscous oil: ¹H NMR (500 MHz, CD₃OD) δ 1.20 (d, J = 7 Hz, 3 H), 2.28 (m, 2 H), 2.60 (m, 2 H), 3.18 (bs, 6 H), 3.35- 3.45 (m, 2 H), 3.60- 3.95 (m, 2
20 H), 4.15 (m, 1 H), 4.32 (m, 1 H), 4.42 (m, 1 H), 5.00 (bm, 2 H), 7.20 (bs, 5 H), and 7.40 ppm (bs, 5 H); ¹⁹F NMR (470 MHz, CD₃OD) δ -10.72 ppm (s, 3 F).

4-Oxo-3(S)-{2(R,S)-[7-oxo-4-(3-phenyl-propionyl)-6(S)-(3-phenyl-propionylamino)-[1,4]diazepan-1-yl]-propionylamino}-butyric acid (115):

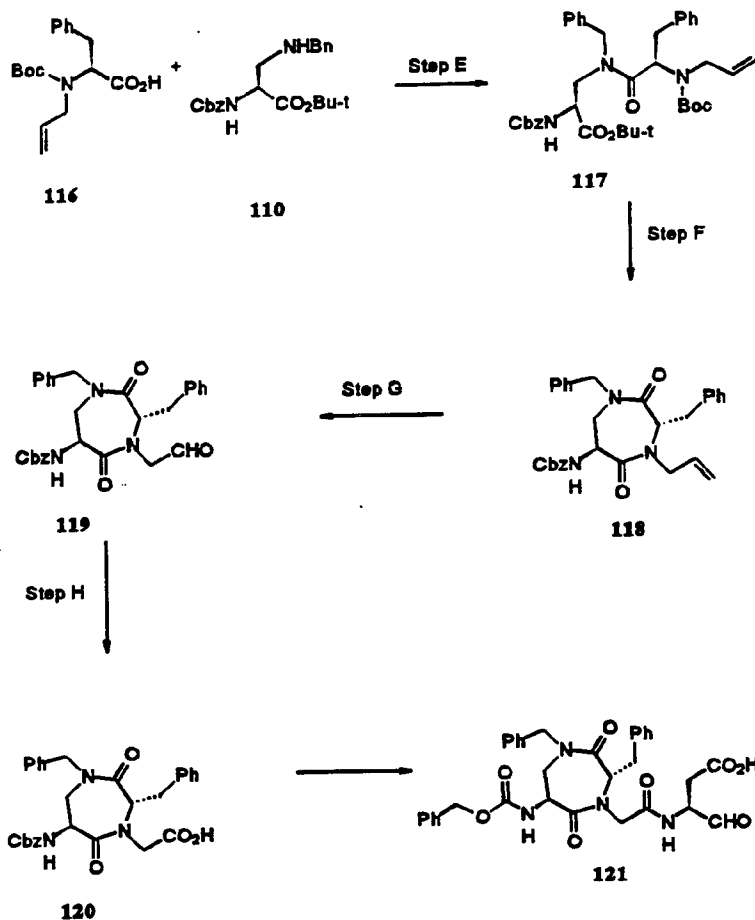
Step D. A suspension of 2(R,S)-[4-benzyl-7-oxo-6(S)-(N-benzyloxycarbonylamino)-[1,4]diazepan-1-yl]-propionic acid methyl ester (112b; 0.22 g, 0.49 mmol) and 20% Pd(OH)₂ on carbon (50 mg) in ethanol was
30 stirred under hydrogen atmosphere for 7 hours. The solvent was evaporated under reduced pressure and the

- 260 -

residue dissolved in dichloromethane (20 mL) then treated with triethylamine (1 mL) and dihydrocinnamoyl chloride (170 mg, 1 mmol). The resulting mixture was allowed to stir overnight then
5 diluted with ethyl acetate and washed with 1 N NaOH. The organic layer was dried (MgSO_4), filtered and evaporated to give an oil. Chromatography (silica-gel, 4:1 hexane: ethyl acetate) gave 0.175 g (75% yield) of 113 as an oil.

10 **Step C.** A 0.15 g sample of 113 (0.32 mmol) was dissolved in methanol, treated with 1 M LiOH (0.32 mL), stirred at 40 °C overnight then evaporated to dryness. The residue was azeotroped with ethanol (2 x 10 mL), acetonitrile (2 x 10 mL), benzene (2 x 10
15 mL) then dried under vacuum. The resulting residue was converted to 115 by a method similar to that described in example 3, compound K (steps A, B, and C).

- 261 -



3-{2-[2,4-Dibenzyl-3,7-dioxo-6-(N-benzyloxycarbonylamino)-[1,4]diazepan-1-yl]-acetylamino}-4-oxo-butyric acid (121):

- 5 **Step E.** A solution of tert-butyl-2-N-carbobenzoyl-3-N-benzyl-(S)-2,3-diaminopropionate (110; 1.77 g, 4.6 mmol), N-allyl-N-tert-butoxycarbonyl-(S)-phenylalanine (116; 1.04 g, 4.8 mmol), HOBT (0.74 g, 5.5 mmol) and EDC (1.33 g, 6.9 mmol) in
- 10 dichloromethane (50 mL) was allowed to stir at 25 °C for 16 h then diluted with dichloromethane (100 mL) and washed with water. The organic layer was dried (MgSO₄), filtered and evaporated to give an oil. Chromatography (silica-gel, 85: 15 hexane: ethyl

- 262 -

acetate) gave 1.34 g (43% yield) of 117 as a colorless viscous oil.

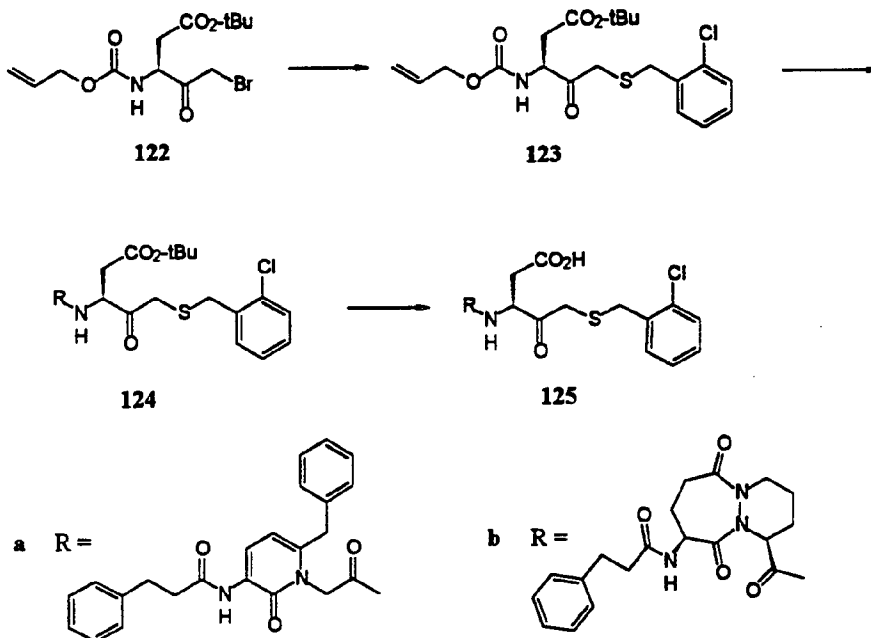
5 Step F. A 1.34 g sample of 117 was dissolved in dichloromethane (3 mL) and treated with a 50% solution of trifluoroacetic acid in dichloromethane (20 mL). After 1.5 h, the solvent was removed under reduced pressure and the residue dried under vacuum then dissolved in dichloromethane (50 mL) and combined with 4-methylmorpholine (0.2 mL, 2 mmol),
10 HOBT (0.27 g, 2 mmol) and EDC (0.8 g, 4 mmol). The mixture was stirred overnight at 25 °C then diluted with dichloromethane and washed with water. The organic layer was dried (MgSO₄), filtered and evaporated to give an oil. Chromatography (silica-gel, 7:3 hexane: ethyl acetate) gave 0.8 g (80%
15 yield) of 118 as a viscous oil.

 Step G. A 0.8 g sample of 118 was dissolved in methanol (40 mL), cooled to -78 °C and saturated with ozone until the solution was blue in color. The
20 excess ozone was removed by purging with argon then dimethylsulfide (5 mL) was added and the mixture allowed to warm to 25 °C and stir 3 h. Solvent removal and chromatography (silica-gel, 1:1 hexane: ethyl acetate) gave 0.74 g (74% yield) of 119 as a
25 white solid.

 Step H. A 0.2 g sample (0.4 mmol) of 119 was dissolved in acetone (25 mL), cooled to 0 °C and treated dropwise with a solution of Jones reagent until the orange color persisted. 2-Propanol (5 mL)
30 was then added to the mixture and the resulting solution filtered through Celite and washed with acetone. Solvent removal gave a green-white solid that was dried under vacuum to give 120. The resulting residue was converted to 121 by a method

- 263 -

similar to that described in example 3, compound K (steps A, B, and C). Chromatography (SiO₂, 95: 4.5: 0.5 dichloromethane: methanol: acetic acid eluent) gave 85 mg (53% yield) of cream colored solid which was identified as 3-{2-[2,4-dibenzyl-3,7-dioxo-6-(N-benzyloxycarbonylamino)-[1,4]diazepan-1-yl-acetylamino}-4-oxo-butyric acid (121) on the basis of the following spectral data: ¹H NMR (500 MHz, CD₃OD) δ 2.38 (m, 1 H), 2.45 (m, 1 H), 3.21 (bs, 2 H), 3.32-3.39 (bm, 6 H), 3.85 (m, 1 H), 4.05 (m, 1 H), 4.21 (bm, 1 H), 4.31 (bs, 1 H), 4.45 (dm, J = 11 Hz, 1 H), 4.95 (bs, 4 H), 7.20 (bs, 5 H), and 7.33- 7.45 ppm (m, 5 H); ¹⁹F NMR (470 MHz, CD₃OD) d -10.62 ppm (s, 3 F).



15 t-Butyl (3*S*) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxo-pentanoate (123). Potassium fluoride (273mg, 4.70mmol) and then 2-chlorophenylmethyl thiol (373mg, 2.35mmol) were added

- 264 -

to a stirred solution of (3S) t-butyl N-(allyloxycarbonyl)-3-amino-5-bromo-4-oxo-pentanoate (122; 749mg, 2.14mmol; WO 93 16710) in dimethylformamide (20ml). The mixture was stirred for 3.5h, quenched with water (50ml) and extracted with ethyl acetate (2 x 50ml). The combined organic extracts were washed with water (4 x 50ml) then brine (50ml). They were dried (MgSO₄) and concentrated to afford an oil which was purified by flash chromatography (10-35% ethyl acetate / hexane) to afford 832 mg (91%) of a colourless solid: mp. 45-6 °C; $[\alpha]_D^{20}$ -19.0° (c 1.0, CH₂Cl₂); IR (film) 3340, 2980, 2935, 1725, 1712, 1511, 1503, 1474, 1446, 1421, 1393, 1368, 1281, 1244, 1157, 1052, 1040, 995, 764, 739; ¹H NMR (CDCl₃) δ 7.36 (2H, m), 7.21 (2H, m), 5.91 (2H, m), 5.27 (2H, m), 4.76 (1H, m), 4.59 (2H, d), 3.78 (2H, s), 3.36 (2H, m), 2.91 (1H, dd), 2.74 (1H, dd), 1.43 (9H, s). Anal. Calcd for C₂₀H₂₆ClNO₅S: C, 56.13; H, 6.12; N, 3.27; S, 7.49. Found: C, 56.08; H, 6.11; N, 3.26; S, 7.54. MS (C.I.) 430/28 (M⁺ + 1, 3%), 374/2 (100).

t-Butyl (3S) 3(2(6-benzyl-1,2-dihydro-2-oxo-3(3-phenylpropionylamino)-1-pyridyl)acetylamino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124a). 6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-pyridyl acetic acid (52b; 300mg, 0.76mmol) in THF (7ml) was stirred with 1-hydroxybenzotriazole (205mg, 1.52mmol) and 1-(3-dimethylaminopropyl-3-ethylcarbodiimide hydrochloride). After 3 min, water (12 drops) was added and the mixture stirred 10min then treated with t-butyl (3S) N-(allyloxycarbonyl)-3-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate

- 265 -

(123) (325mg, 0.76mmol), bis (triphenylphosphine) palladium II chloride (20mg) and tributyltin hydride (0.6ml, 2.28mmol). The mixture was stirred for 5h at room temperature, poured into ethyl acetate and washed with aqueous 1M HCl (x2), aqueous sodium bicarbonate, brine, dried (MgSO₄) and concentrated. The residue was triturated with pentane and the supernatant discarded. Chromatography (silica gel, 50% ethyl acetate/hexane) afforded a colourless foam (439mg, 81%): $[\alpha]_D^{21}$ -18.3 ° (c 0.5, CH₂Cl₂); IR (KBr) 3356, 3311, 1722, 1689, 1646, 1599, 1567, 1513, 1367, 1154; ¹H NMR (CDCl₃) δ 8.39 (1H, d), 8.23 (1H, s), 7.24 (14H, m), 6.16 (1H, d), 4.95 (1H, m), 4.63 (2H, m), 4.02 (2H, s), 3.74 (2H, s), 3.27 (2H, s), 2.85 (6H, m), 1.40 (9H, s). Anal. Calcd for C₃₃H₄₂ClN₃O₆S: C, 65.39; H, 5.91; N, 5.87. Found: C, 65.51; H, 5.99; N, 5.77.

t-Butyl[3*S*(1*S*,9*S*)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazine[1,2-*a*][1,2]diazepine-1-carboxamido-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124b) was prepared by a similar method as 124a from the thioether 123 and 3*S*(1*S*,9*S*)-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionylamino)-6H-pyridazino[1,2-*a*][1,2]diazepine-1-carboxylic acid (45a) to afford 452mg (50%) of colourless foam: mp 55-7 °C; $[\alpha]_D^{22}$ -94.0° (c 0.12, CH₂Cl₂); IR (KBr) 3288, 2934, 1741, 1722, 1686, 1666, 1644, 1523, 1433, 1260, 1225, 1146, 757; ¹H NMR (CDCl₃) δ 7.35 (3H, m), 7.20 (7H, m), 6.46 (1H, d), 5.21 (1H, m), 4.97 (2H, m), 4.56 (1H, m), 3.75 (2H, s), 3.25 (3H, m), 2.93 (5H, m), 2.71 (1H,

- 266 -

dd), 2.55 (2H, m), 2.30 (1H, m), 1.92 (3H, m), 1.66 (2H, m), 1.42 (9H, s). Anal. Calcd for $C_{35}H_{43}ClN_4O_7S$. 0.25H₂O: C, 59.73; H, 6.23; Cl, 5.04; N, 7.96; S, 4.56. Found: C, 59.73; H, 6.19; Cl, 5.10; N, 7.79; S, 4.58. MS (-FAB) 697 (M-1, 100).

(3S) 3(2(6-Benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoic acid (125a). t-Butyl-3(2(6-benzyl-1,2-dihydro-2-oxo-3-(3-phenylpropionylamino)-1-pyridyl)acetyl-amino-5-(2-chlorophenylmethylthio)-4-oxopentanoate (124a) (400mg, 0.56mmol) in dichloromethane (3ml) at 0 °C was treated with trifluoroacetic acid (3ml) and stirred at 0 °C for 1h and room temperature for 0.5h. The solution was concentrated then redissolved in dichloromethane and reconcentrated. This procedure was repeated three times. The residue was stirred in ether for 1hr and filtered to yield a colourless solid (364mg, 99%): mp. 165-7 °C; $[\alpha]_D^{22}$ -27.7 ° (c 0.2, CH₂Cl₂); IR (KBr) 3289, 1712, 1682, 1657, 1645, 1593, 1562, 1527, 1497, 1416, 1203, 1182; ¹H NMR (CDCl₃) δ 8.47 (1H, d), 8.21 (1H, s), 7.70 (1H, d), 7.22 (14H, m), 6.24 (1H, d), 5.03 (1H, m), 4.65 (2H, m), 4.06 (2H, s), 3.69 (2H, m), 3.23 (2H, m), 2.88 (6H, m).

[3S(1S, 9S)]-3-(6,10-dioxo-1,2,3,4,7,8,9,10-octahydro)-9-(3-phenylpropionyl-amino)-6H-pyridazine[1,2-a][1,2]diazepine-1-carboxamido-5-(2-chlorophenyl-methylthio)-4-oxopentanoic acid (125b), was prepared by a similar method as 125a from the t-butyl ester 124b to afford

- 267 -

362mg (93%) of colourless powder: mp 76-80 °C; $[\alpha]_D^{21}$
-134 ° (c 0.10, MeOH); IR (KBr) 3309, 2935, 1725,
1658, 1528, 1445, 1417, 1277, 1219, 1175; ^1H NMR (D_6 -
DMSO) δ 8.80 (1H, d), 8.19 (1H, d), 7.31 (9H, m),
5 5.09 (1H, m), 4.74 (1H, m), 4.63 (1H, m), 4.35 (1H,
m), 3.76 (2H, m), 3.28 (3H, m), 2.80 (5H, m), 2.52
(4H, m), 2.16 (2H, m), 1.90 (3H, m). Anal. Calcd for
 $\text{C}_{31}\text{H}_{35}\text{Cl}_2\text{N}_4\text{O}_7\text{S} \cdot 0.25\text{H}_2\text{O}$: C, 57.49; H, 5.53; N, 8.65; S,
4.95. Found: C, 57.35; H, 5.43; N, 8.45; S, 4.88.
10 MS (-FAB) 641 (M-1, 100).

The data of the examples above demonstrate
that compounds according to this invention display
inhibitory activity towards IL-1 β Converting Enzyme.

15 Insofar as the compounds of this invention
are able to inhibit ICE in vitro and furthermore, may
be delivered orally to mammals, they are of evident
clinical utility for the treatment of IL-1 mediated
diseases. These tests are predictive of the
20 compounds ability to inhibit ICE in vivo.

While we have described a number of
embodiments of this invention, it is apparent that
our basic constructions may be altered to provide
other embodiments which utilize the products and
25 processes of this invention. Therefore, it will be
appreciated that the scope of this invention is to be
defined by the appended claims, rather than by the
specific embodiments which have been presented by way
of example.

- 268 -

CLAIMS

We claim:

1. An ICE inhibitor comprising:
 - (a) a first and a second hydrogen
5 bonding moiety, each of said moieties being capable
of forming a hydrogen bond with a different backbone
atom of ICE, said backbone atom being selected from
the group consisting of the carbonyl oxygen of
Arg-341, the amide -NH- group of Arg-341, the
10 carbonyl oxygen of Ser-339 and the amide -NH- group
of Ser-339;
 - (b) a first and a second moderately
hydrophobic moiety, said moieties each being capable
of associating with a separate binding pocket of ICE
15 when the inhibitor is bound thereto, said binding
pocket being selected from the group consisting of
the P2 binding pocket, the P3 binding pocket, the P4
binding pocket and the P' binding pocket; and
 - (c) an electronegative moiety
20 comprising one or more electronegative atoms, said
atoms being attached to the same atom or to adjacent
atoms in the moiety and said moiety being capable of
forming one or more hydrogen bonds or salt bridges
with residues in the P1 binding pocket of ICE.
- 25 2. The ICE inhibitor according to claim 1,
wherein said inhibitor is characterized by a neutral
or favorable enthalpic contribution from the sum of
all electrostatic interactions between the inhibitor
and ICE when the inhibitor is bound thereto.
- 30 3. The ICE inhibitor according to claim 1,
wherein said inhibitor has a molecular weight less
than or equal to about 700 Daltons.

- 269 -

4. The ICE inhibitor according to claim 3, wherein said inhibitor has a molecular weight between about 400 and about 600 Daltons.

5. The ICE inhibitor according to claim 1, wherein said inhibitor further comprises less than two secondary amide bonds.

6. The ICE inhibitor according to claim 1, wherein said inhibitor further comprises less than two groups selected from the set consisting of secondary amide groups and carbamate groups.

7. The ICE inhibitor according to claim 1, wherein said inhibitor further comprises a polysubstituted cyclic group having between three and seven substituents, said cyclic group not comprising the first or second moderately hydrophobic moiety or the electronegative moiety.

8. The ICE inhibitor according to claim 1 or 7, wherein said inhibitor is characterized by a strain energy of binding of said inhibitor to ICE less than or equal to about 10 kcal/mole.

9. The ICE inhibitor according to claim 1 or 7, wherein when said inhibitor is bound to ICE at least two of the following four conditions 1) through 4) are met:

1) one of said moderately hydrophobic moieties associates with the P2 binding pocket of ICE, in such a way that:

a) the distance from the center of mass of the moderately hydrophobic moiety in the P2

- 270 -

binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 7.1Å and about 12.5Å;

5 b) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 6.0Å and about 12Å; and

10 c) the distance from the center of mass of the moderately hydrophobic moiety in the P2 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 3.7Å and about 9.5Å;

2) one of said moderately hydrophobic moieties associates with the P3 binding pocket of ICE in such a way that:

15 a) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 3.9Å and about 9.5Å;

20 b) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the amide nitrogen of Arg-341 of ICE is between about 5.4Å and about 11Å; and

25 c) the distance from the center of mass of the moderately hydrophobic moiety in the P3 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 7.0Å and about 13Å;

3) one of said moderately hydrophobic moieties associates with the P4 binding pocket of ICE in such a way that:

30 a) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 4.5Å and about 7.5Å;

 b) the distance from the center of mass of the moderately hydrophobic moiety in the P4

- 271 -

binding pocket to the amide nitrogen of Arg-341 of ICE is between about 5.5Å and about 8.5Å; and

5 c) the distance from the center of mass of the moderately hydrophobic moiety in the P4 binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 8Å and about 11Å; and

4) one of said moderately hydrophobic moieties associates with the P' binding pocket of ICE in such a way that:

10 a) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the carbonyl oxygen of Arg-341 of ICE is between about 11Å and about 16Å;

15 b) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the amide nitrogen of Arg-341 of ICE is between about 10Å and about 15Å; and

20 c) the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the carbonyl oxygen of Ser-339 of ICE is between about 8Å and about 12Å.

10. The ICE inhibitor according to claim 1 or 7, wherein when said inhibitor is bound to ICE, said moderately hydrophobic moieties separately
25 associate with the P' binding pocket of ICE and the P2 binding pocket of ICE and the distance from the center of mass of the moderately hydrophobic moiety in the P' binding pocket to the center of mass of the moderately hydrophobic moiety in the P2 binding
30 pocket is between about 6.5Å and about 13Å.

11. The ICE inhibitor according to claim 1 or 7, wherein when said inhibitor is bound to ICE,

- 272 -

said moderately hydrophobic moieties separately
associate with the P' binding pocket of ICE and the
P3 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
5 in the P' binding pocket to the center of mass of the
moderately hydrophobic moiety in the P3 binding
pocket is between about 6Å and about 15Å.

12. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
10 said moderately hydrophobic moieties separately
associate with the P' binding pocket of ICE and the
P4 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
in the P' binding pocket to the center of mass of the
15 moderately hydrophobic moiety in the P4 binding
pocket is between about 14Å and about 22Å.

13. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said moderately hydrophobic moieties separately
20 associate with the P2 binding pocket of ICE and the
P3 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
in the P2 binding pocket to the center of mass of the
moderately hydrophobic moiety in the P3 binding
25 pocket is between about 5.5Å and about 13Å.

14. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said moderately hydrophobic moieties separately
associate with the P2 binding pocket of ICE and the
30 P4 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety

- 273 -

in the P2 binding pocket to the center of mass of the moderately hydrophobic moiety in the P4 binding pocket is between about 9Å and about 17Å.

15 15. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said moderately hydrophobic moieties separately
associate with the P3 binding pocket of ICE and the
P4 binding pocket of ICE and the distance from the
center of mass of the moderately hydrophobic moiety
10 in the P3 binding pocket to the center of mass of the
moderately hydrophobic moiety in the P4 binding
pocket is between about 7.5Å and about 17Å.

15 16. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said first hydrogen bonding moiety forms a hydrogen
bond with the carbonyl oxygen of Ser-339 of ICE and
said second hydrogen bonding moiety forms a hydrogen
bond with the carbonyl oxygen of Arg-341 of ICE and
wherein the distance between said hydrogen bonding
20 moieties is between about 5Å and about 7.5Å.

25 17. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,
said first hydrogen bonding moiety forms a hydrogen
bond with the carbonyl oxygen of Ser-339 of ICE and
said second hydrogen bonding moiety forms a hydrogen
bond with the amide -NH- group of Arg-341 of ICE and
wherein the distance between said moieties is between
about 2.5Å and about 5Å.

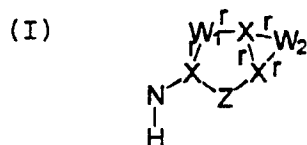
30 18. The ICE inhibitor according to claim 1
or 7, wherein when said inhibitor is bound to ICE,

- 274 -

said first hydrogen bonding moiety forms a hydrogen bond with the carbonyl oxygen of Arg-341 of ICE and said second hydrogen bonding moiety forms a hydrogen bond with the amide -NH- group of Arg-341 of ICE and wherein the distance between said hydrogen bonding moieties is between about 2.5Å and about 4Å.

19. An ICE inhibitor comprising:

(a) a scaffold of formula I:



wherein:

each X is independently C or N;

Z is CO or SO₂;

W₁ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

W₂ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

each bond labeled r is independently a single or a double bond;

H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen

- 275 -

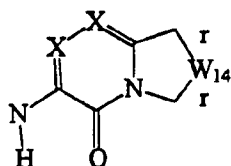
bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

20. The ICE inhibitor according to claim 19, wherein said scaffold has the formula:

(IA)



wherein:

each X is independently C or N;

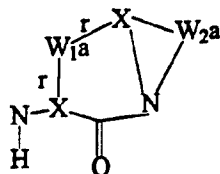
W₁₄ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or

- 276 -

unsaturated and said chain comprising two ends which
are covalently bound to two different C atoms through
bonds r; and
each bond labeled r is independently a single or a
5 double bond.

21. The ICE inhibitor according to claim 19,
wherein said scaffold has the formula:

(IB)



wherein:

10

X is C or N;

15

W_{1a} is a straight chain comprising 1-3
covalently bound members independently selected from
the group consisting of C, N, S and O, said covalent
bonds between said members being independently
saturated or unsaturated and said chain comprising
two ends which are covalently bound to two different
X atoms through bonds r;

20

W_{2a} is a straight chain comprising 3-4
covalently bound members independently selected from
the group consisting of C, N, S and O, said chain
comprising two ends which are covalently bound to two
different atoms to form an aryl or heteroaromatic
ring therewith; and

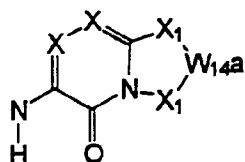
25

each bond labeled r is independently a
single or a double bond.

- 277 -

22. The ICE inhibitor according to claim 19,
wherein said scaffold has the formula:

(IC)

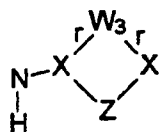


wherein:

- 5 each X is independently C or N;
 each X₁ is independently C, N, or O; and
 W_{14a} is a straight chain comprising 1-3
covalently bound members independently selected from
the group consisting of C, N, S and O, said covalent
10 bonds between said members being saturated or
unsaturated and said chain comprising two ends which
are covalently bound to two different X₁ atoms to
form a non-aromatic ring therewith.

23. An ICE inhibitor comprising:
a scaffold of formula II:

(II)



wherein:

- each X is independently C or N;
 Z is CO or SO₂;
20 W₃ is a straight chain comprising 2-4
covalently bound members independently selected from
the group consisting of C, N, S and O, said covalent
bonds between said members being independently
saturated or unsaturated and said chain comprising
25 two ends which are covalently bound to two different
X atoms through bonds r;
 each bond labeled r is independently a
single or a double bond;

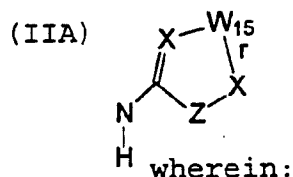
- 278 -

H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(a) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(b) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

24. The ICE inhibitor according to claim 23, wherein said scaffold has the formula:



each X is independently C or N;
Z is CO or SO₂;

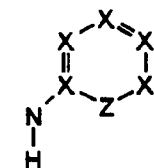
- 279 -

W₁₅ is a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms; and

the bond labeled r is a single or a double bond.

25. The ICE inhibitor according to claim 23, wherein said scaffold has the formula:

(IIB)

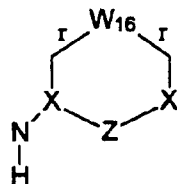


wherein:

each X is independently C or N; and
Z is CO or SO₂.

26. The ICE inhibitor according to claim 23, wherein said scaffold has the formula:

(IIC)



wherein:

each X is independently C or N;
Z is CO or SO₂;

W₁₆ is a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising

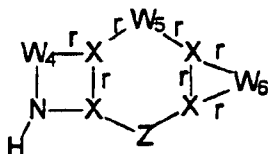
- 280 -

two ends which are covalently bound to two different C atoms through bonds r; and

each bond labeled r is independently a single or a double bond.

- 5 27. An ICE inhibitor comprising:
 (a) a scaffold of formula III:

(III)



, wherein:

10 each X is independently C or N;

 Z is CO or SO₂;

 W₄ is a straight chain comprising 2-4 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently
 15 saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms;

 W₅ is a direct bond or a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being
 20 independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

 W₆ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently
 25 saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

30 saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

- 281 -

each bond labeled r is independently a single or a double bond;

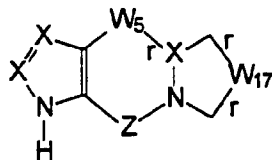
H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

28. The ICE inhibitor according to claim 27, wherein said scaffold has the formula:

(IIIA)



wherein:

- 282 -

each X is independently C or N;

Z is CO or SO₂;

W₅ is a direct bond or a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms;

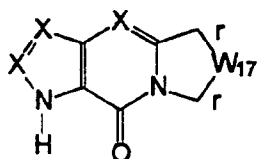
W₁₇ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and

each bond labeled r is independently a single or a double bond.

29. The ICE inhibitor according to claim 27,

wherein:

(IIIB)



wherein:

each X is independently C or N;

W₁₇ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and

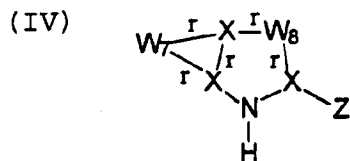
each bond labeled r is independently a

- 283 -

single or a double bond.

30. An ICE inhibitor comprising:

(a) a scaffold of formula IV:



wherein:

each X is independently C or N;

Z is CO or SO₂;

W₇ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

W₈ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated, and said chain comprising two ends which are covalently bound to two different X atoms through bonds r;

each bond labeled r is independently a single or a double bond;

H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide

- 284 -

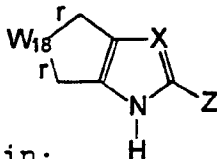
-NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

31. The ICE inhibitor according to claim 30, wherein said scaffold has the formula:

(IVA)



wherein:

each X is independently C or N;

Z is CO or SO₂;

W₁₈ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and

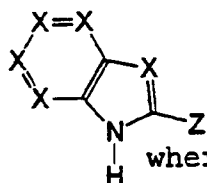
each bond labeled r is independently a

- 285 -

single or a double bond.

32. The ICE inhibitor according to claim 30, wherein said scaffold has the formula:

(IVB)

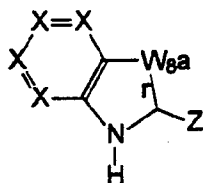


wherein:

each X is independently C or N; and
Z is CO or SO₂.

33. The ICE inhibitor according to claim 30, wherein said scaffold has the formula:

(IVC)



wherein:

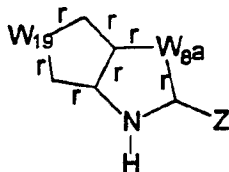
each X is independently C or N;
Z is CO or SO₂;

W_{8a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms; and
the bond labeled r is a single or a double bond.

- 286 -

34. The ICE inhibitor according to claim 30, wherein said scaffold has the formula:

(IVD)



wherein:

5

Z is CO or SO₂;

10

W_{8a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r;

15

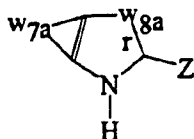
W₁₉ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r; and

20

each bond labeled r is independently a single or a double bond.

35. The ICE inhibitor according to claim 30, wherein said scaffold has the formula:

(IVE)



25

wherein:

Z is CO or SO₂;

W_{8a} is a straight chain comprising 1-3 covalently bound members independently selected from

- 287 -

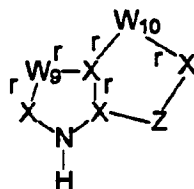
the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms;

5 W_{7a} is a straight chain comprising 3 covalently bound members independently selected from the group consisting of C, N, S and O, said chain comprising two ends which are covalently bound to two different C atoms to form an aryl ring therewith; and
10 the bond labeled r is a single or a double bond.

36. An ICE inhibitor comprising:

a) a scaffold of formula V:

15 (V)



wherein:

each X is independently C or N;

Z is CO or SO₂;

20 W_9 is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising
25 two ends which are covalently bound to two different X atoms through bonds r;

W_{10} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent
30 bonds between said members being independently saturated or unsaturated and said chain comprising

- 288 -

two ends which are covalently bound to two different X atoms through bonds r;

each bond labeled r is independently a single or a double bond;

5 H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the
10 carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

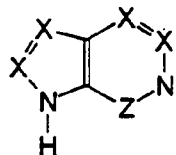
 b) a first and a second moderately hydrophobic moiety, said moieties each being
15 covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group
20 consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

 c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the
25 moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

37. The ICE inhibitor according to claim 36,
30 wherein said scaffold has the formula:

- 289 -

(VA)



wherein:

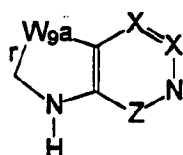
each X is independently C or N; and

Z is CO or SO₂.

5

38. The ICE inhibitor according to claim 36, wherein said scaffold has the formula:

(VB)



wherein:

each X is independently C or N;

Z is CO or SO₂;

W_{9a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms; and

10

15

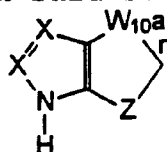
20

the bond labeled r is a single or a

double bond.

39. The ICE inhibitor according to claim 36, wherein said scaffold has the formula:

(VC)



wherein:

each X is independently C or N;

25

- 290 -

Z is CO or SO₂;

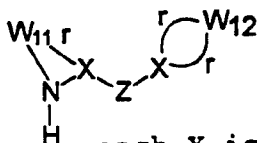
W_{10a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different X atoms; and

the bond labeled r is a single or a double bond.

40. An ICE inhibitor comprising:

(a) a scaffold of formula VI:

(VI)



wherein:

each X is independently C or N;

Z is CO or SO₂;

W₁₁ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms to form a ring which may optionally be benzofused or pyridinofused;

W₁₂ is a straight chain comprising 4-6 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to the indicated X atom through bonds r;

each bond labeled r is independently a

- 291 -

single or a double bond;

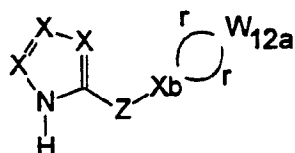
H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

41. The ICE inhibitor according to claim 40, wherein said scaffold has the formula:

(VIA)



wherein:

each X and X_b is independently C or N;

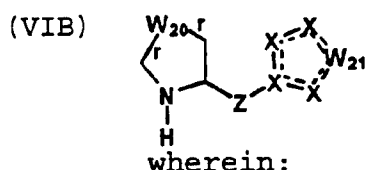
- 292 -

Z is CO or SO₂;

W_{12a} is a straight chain comprising 4-6 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to the indicated X_b atom through bonds r; and

each bond labeled r is independently a single or a double bond.

42. The ICE inhibitor according to claim 40, wherein said scaffold has the formula:



each X is independently C or N;

Z is CO or SO₂;

W₂₀ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different C atoms through bonds r;

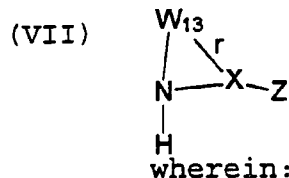
W₂₁ is a straight chain comprising 1-2 covalently bound members independently selected from the group consisting of C, N, S and O, said chain comprising two ends which are covalently bound to two different C atoms to form an aryl ring therewith; and

each bond labeled r is independently a single or a double bond.

- 293 -

43. An ICE inhibitor comprising:

(a) a scaffold of formula VII:



X is C or N;

Z is CO or SO₂;

W₁₃ is a straight chain comprising 3-5 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms;

the bond labeled r is a single or a double bond;

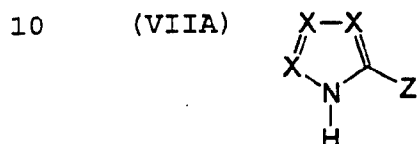
H is a first hydrogen bonding moiety and Z is a second hydrogen bonding moiety, each of said moieties being capable of forming a hydrogen bond with a different backbone atom of ICE, said backbone atom being selected from the group consisting of the carbonyl oxygen of Arg-341, the amide -NH- group of Arg-341, the carbonyl oxygen of Ser-339 and the amide -NH- group of Ser-339;

(b) a first and a second moderately hydrophobic moiety, said moieties each being covalently bound to said scaffold and each being capable of associating with a separate binding pocket of ICE when the inhibitor is bound thereto, said binding pocket being selected from the group consisting of the P2 binding pocket, the P3 binding pocket, the P4 binding pocket and the P' binding pocket; and

- 294 -

(c) an electronegative moiety comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

44. The ICE inhibitor according to claim 43, wherein said scaffold has the formula:

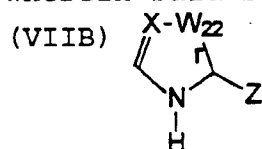


wherein:

each X is independently C or N; and

Z is CO or SO₂.

45. The ICE inhibitor according to claim 43, wherein said scaffold has the formula:



wherein:

X is C or N;

Z is CO or SO₂;

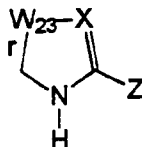
20 W₂₂ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms; and

the bond labeled r is a single or a double bond.

- 295 -

46. The ICE inhibitor according to claim 43, wherein said scaffold has the formula:

(VIIC)



wherein:

X is C or N;

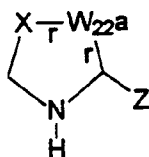
Z is CO or SO₂;

W₂₃ is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms; and

the bond labeled r is a single or a double bond.

47. The ICE inhibitor according to claim 43, wherein said scaffold has the formula:

(VIID)



wherein:

X is C or N;

Z is CO or SO₂;

W_{22a} is a straight chain comprising 1-3 covalently bound members independently selected from the group consisting of C, N, S and O, said covalent bonds between said members being independently saturated or unsaturated and said chain comprising two ends which are covalently bound to two different atoms through bonds r; and

- 296 -

each bond labeled r is independently a single or a double bond.

48. An ICE inhibitor comprising:

- a) a scaffold comprising any
5 monocyclic, bicyclic or tricyclic system, wherein
each ring of said system comprises 5-7 members, said
system comprising C, N, O or S, said system being
aromatic or non-aromatic and comprising a central
ring, wherein the distance between the centroid of
10 said central ring and the alpha carbon of Cys-285 of
ICE is between about 5.0Å and about 6.0Å when the
inhibitor is bound to ICE and the distance between
the centroid of said central ring and the alpha
carbon of His-237 of ICE is between about 5.5Å and
15 about 6.5Å when the inhibitor is bound to ICE;
- b) a first hydrogen bonding moiety and
a second hydrogen bonding moiety, each of said
moieties being capable of forming a hydrogen bond
with a different backbone atom of ICE, said atoms
20 being selected from the group consisting of the
carbonyl oxygen of Arg-341, the amide -NH- group of
Arg-341, the carbonyl oxygen of Ser-339 and the amide
-NH- group of Ser-339;
- c) a first and a second moderately
25 hydrophobic moiety, said moieties each being
covalently bound to said scaffold and each being
capable of associating with a separate binding pocket
of ICE when the inhibitor is bound thereto, said
binding pocket being selected from the group
30 consisting of the P2 binding pocket, the P3 binding
pocket, the P4 binding pocket and the P' binding
pocket; and
- d) an electronegative moiety

- 297 -

comprising one or more electronegative atoms, said atoms being attached to the same atom or to adjacent atoms in the moiety and said moiety being covalently bound to said scaffold and being capable of forming one or more hydrogen bonds or salt bridges with residues in the P1 binding pocket of ICE.

49. A compound represented by the formula:



wherein:

X_1 is CH or N;

g is 0 or 1;

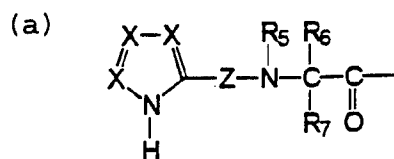
each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

m is 0, 1, or 2;

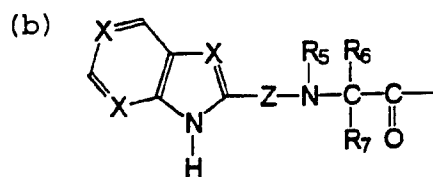
T is -Ar₃, -OH, -CF₃, -CO-CO₂H, -CO₂H or any bioisosteric replacement for -CO₂H;

R_1 is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q₁, at any nitrogen by R₅, or at any atom by =O, -OH, -CO₂H, or halogen, and in which any saturated ring may optionally be unsaturated at one or two bonds:

- 298 -

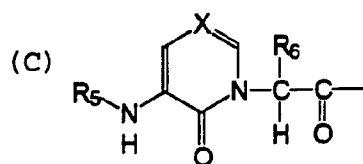


;



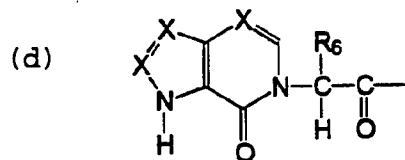
;

5

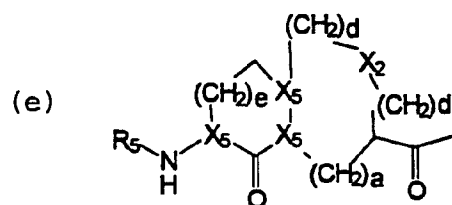


;

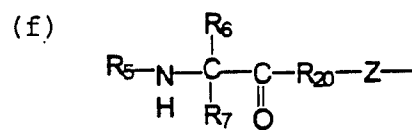
10



;

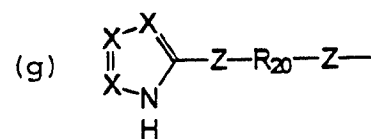


;

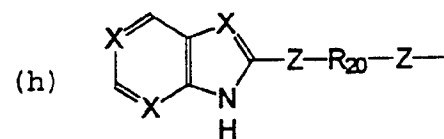


;

15

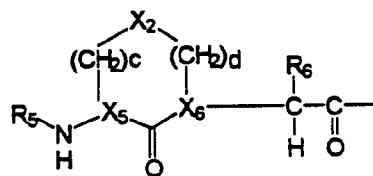
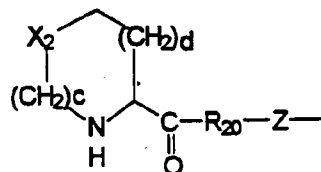
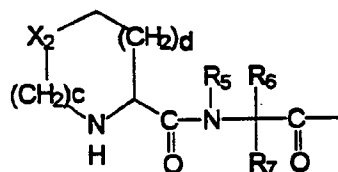
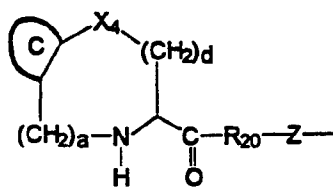
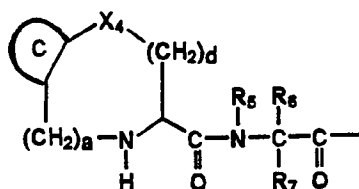
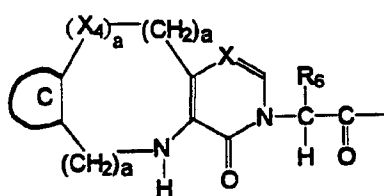
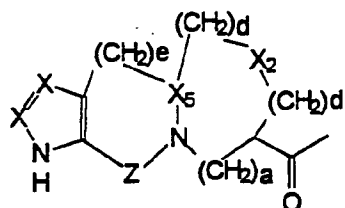


;



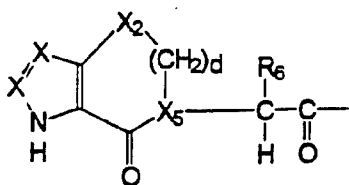
;

20



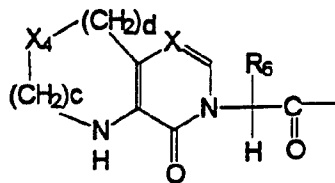
- 300 -

(p)



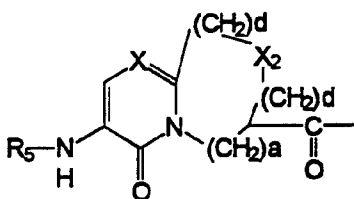
;

(q)



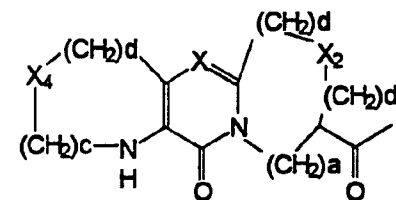
;

(r)



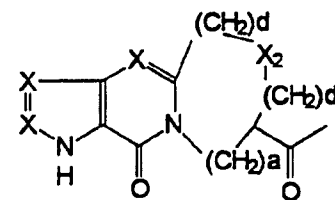
;

(s)



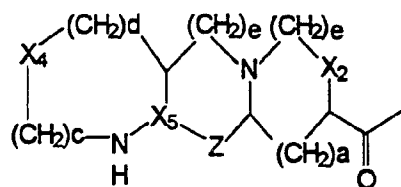
;

(t)



;

(v)

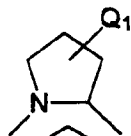


;

- 301 -

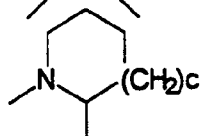
R_{20} is selected from the group consisting of:

(aa1)



;

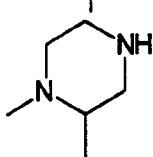
(aa2)



;

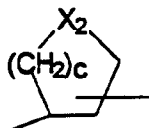
5

(aa3)



;

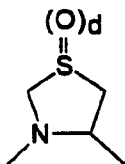
(aa4)



;

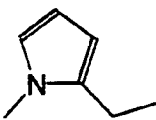
10

(aa5)



;

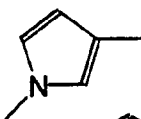
(bb)



;

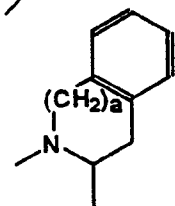
15

(cc)



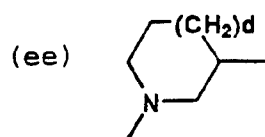
;

(dd)

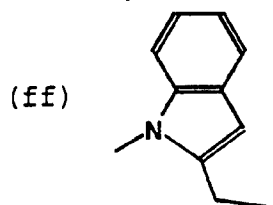


;

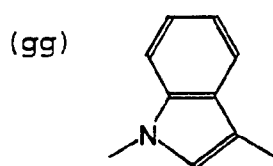
- 302 -



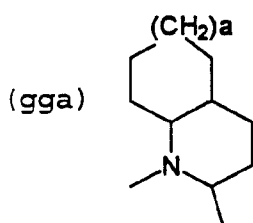
;



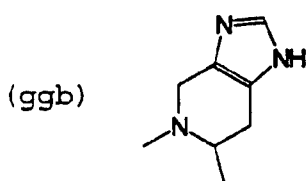
;



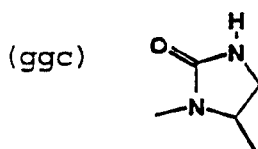
;



;



;



; and

wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

- 303 -

 R_3 is

- CN,
- CH=CH- R_9 ,
- CH=N-O- R_9 ,
- 5 - (CH₂)₁₋₃-T₁- R_9 ,
- CJ₂- R_9 ,
- CO- R_{13} , or
- / R_5
- 10 -CO-CO-N \ R_{10} ;

each R_4 is independently selected from the group consisting of:

- H,
- Ar₁,
- 15 - R_9 ,
- T₁- R_9 , and
- (CH₂)_{1,2,3}-T₁- R_9 ,

each T₁ is independently selected from the group consisting of:

- 20 -CH=CH-,
- O-,
- S-,
- SO-,
- SO₂-,
- 25 -NR₁₀-,
- NR₁₀-CO-,
- CO-,
- O-CO-,
- CO-O-,
- 30 -CO-NR₁₀-,
- O-CO-NR₁₀-,
- NR₁₀-CO-O-,

- 304 -

$\text{-NR}_{10}\text{-CO-NR}_{10}\text{-}$,
 $\text{-SO}_2\text{-NR}_{10}\text{-}$,
 $\text{-NR}_{10}\text{-SO}_2\text{-}$, and
 $\text{-NR}_{10}\text{-SO}_2\text{-NR}_{10}\text{-}$,

5 each R_5 is independently selected from the group consisting of:

-H ,
 -Ar_1 ,
 -CO-Ar_1 ,
 10 $\text{-SO}_2\text{-Ar}_1$,
 -R_9 ,
 -CO-R_9 ,
 -CO-O-R_9 ,
 $\text{-SO}_2\text{-R}_9$,
 15 $\text{-CO-N} \begin{matrix} / \text{Ar}_1 \\ \backslash \text{R}_{10} \end{matrix}$,
 20 $\text{-SO}_2\text{-N} \begin{matrix} / \text{Ar}_1 \\ \backslash \text{R}_{10} \end{matrix}$,
 $\text{-CO-N} \begin{matrix} / \text{R}_9 \\ \backslash \text{R}_{10} \end{matrix}$, and
 25 $\text{-SO}_2\text{-N} \begin{matrix} / \text{R}_9 \\ \backslash \text{R}_{10} \end{matrix}$,

R_6 and R_7 taken together form a saturated 4-8
 member carbocyclic ring or heterocyclic ring
 30 containing -O- , -S- , or -NH- , or R_7 is -H and R_6 is

-H
 -Ar_1 ,

- 305 -

-R₉, or

-(CH₂)_{1,2,3}-T₁-R₉,

5 each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one or two Ar₁ groups;

each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

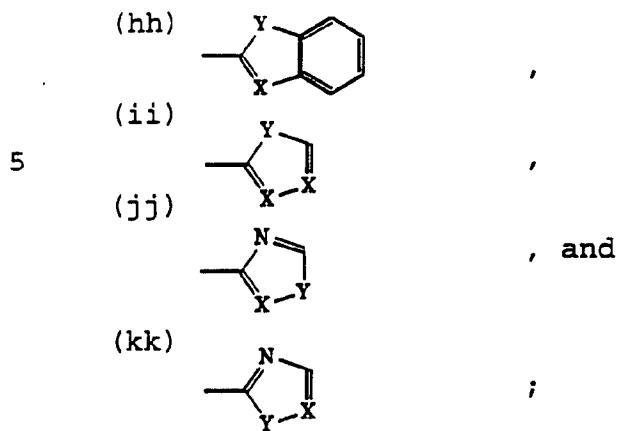
10 each R₁₃ is independently selected from the group consisting of -Ar₂ and -R₄,

15 each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by =O, -OH, perfluoro C₁₋₃ alkyl, or -Q₁;

each Ar₂ is independently selected from the following group, in which any ring may optionally be

- 306 -

substituted by $-Q_1$:



10 Ar_3 is a cyclic group selected from the set consisting of a phenyl ring, a 5-membered heteroaromatic ring, and a 6-membered heteroaromatic ring, said heteroaromatic rings comprising 1-3 heteroatom groups selected from -O-, -S-, -SO-, -SO₂-
 15 , =N-, and -NH-, said cyclic group optionally being singly or multiply substituted with =O, -OH, halogen, perfluoro C₁₋₃ alkyl, or -CO₂H;

each Q_1 is independently selected from the group consisting of

20 $-Ar_1$
 $-R_9$,
 $-T_1-R_9$, and
 $-(CH_2)_{1,2,3}-T_1-R_9$,

provided that when $-Ar_1$ is substituted with a Q_1
 25 group which comprises one or more additional $-Ar_1$ groups, said additional $-Ar_1$ groups are not substituted with Q_1 ;

- 307 -

each X is independently selected from the group consisting of =N-, and =CH-;

each X₂ is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

5 each X₃ is independently selected from the group consisting of -CH₂-, -S-, -SO-, and -SO₂-;

each X₄ is independently selected from the group consisting of -CH₂- and -NH-;

10 each X₅ is independently selected from the group consisting of -CH- and -N-;
| |

15 X₆ is CH or N, provided that when X₆ is N in the R₁ group labeled (o) and X₅ is CH and X₂ is CH₂ the ring of the R₁ group labeled (o) must be substituted by Q₁ or benzofused;

each Y is independently selected from the group consisting of -O- and -S-;

each Z is independently CO or SO₂,

each a is independently 0 or 1,

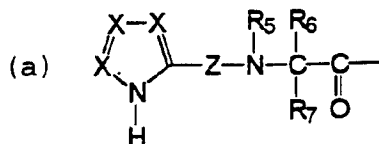
20 each c is independently 1 or 2,

each d is independently 0, 1, or 2, and

each e is independently 0, 1, 2, or 3.

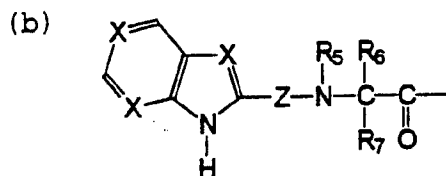
- 308 -

50. The compound according to claims 49 or 80, wherein R_1 is:



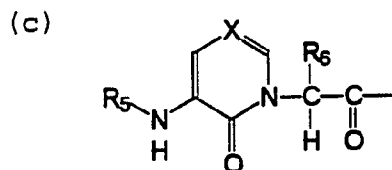
5

51. The compound according to claims 49 or 80, wherein R_1 is:



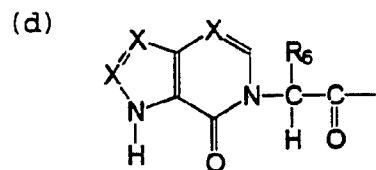
10

52. The compound according to claims 49 or 80, wherein R_1 is:



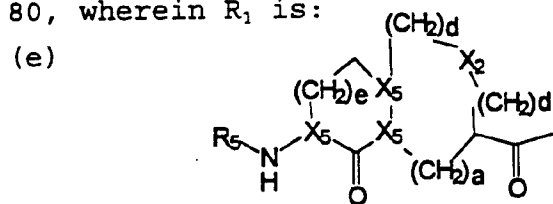
15

53. The compound according to claims 49 or 80, wherein R_1 is:



20

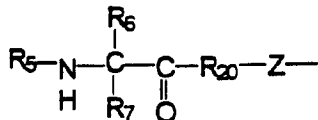
54. The compound according to claims 49 or 80, wherein R_1 is:



- 309 -

55. The compound according to claims 49 or 80, wherein R_1 is:

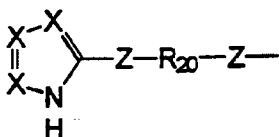
(f)



5

56. The compound according to claims 49 or 80, wherein R_1 is:

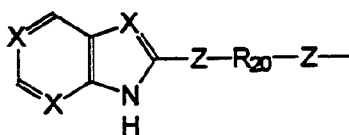
(g)



10

57. The compound according to claims 49 or 80, wherein R_1 is:

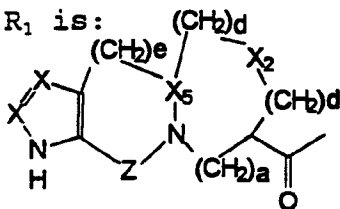
(h)



15

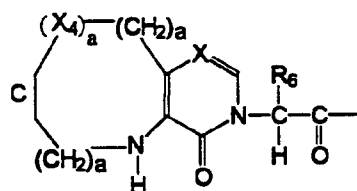
58. The compound according to claims 49 or 80, wherein R_1 is:

(i)



59. The compound according to claims 49 or 80, wherein R_1 is:

(j)

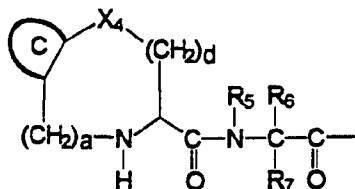


20

- 310 -

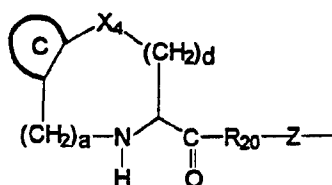
60. The compound according to claims 49 or 80, wherein R_1 is:

(k)



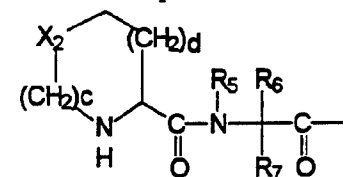
5 61. The compound according to claims 49 or 80, wherein R_1 is:

(l)



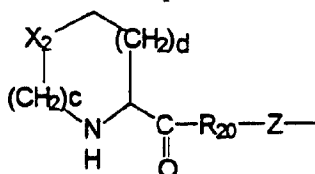
10 62. The compound according to claims 49 or 80, wherein R_1 is:

(m)



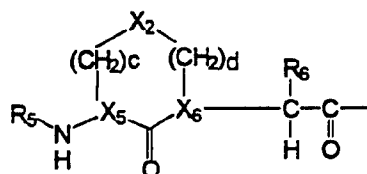
15 63. The compound according to claims 49 or 80, wherein R_1 is:

(n)



20 64. The compound according to claims 49 or 80, wherein R_1 is:

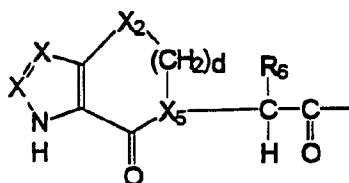
(o)



- 311 -

65. The compound according to claims 49 or 80, wherein R_1 is:

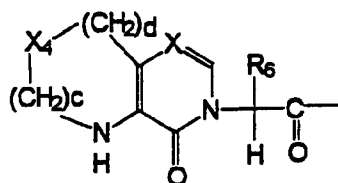
(p)



5

66. The compound according to claims 49 or 80, wherein R_1 is:

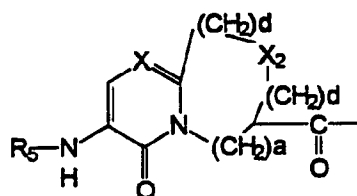
(q)



10

67. The compound according to claims 49 or 80, wherein R_1 is:

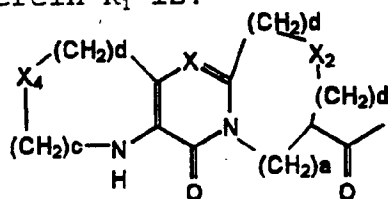
(r)



15

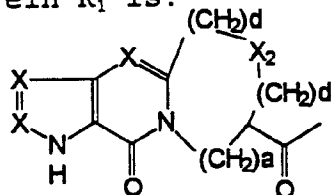
68. The compound according to claims 49 or 80, wherein R_1 is:

(s)



69. The compound according to claims 49 or 80, wherein R_1 is:

(t)

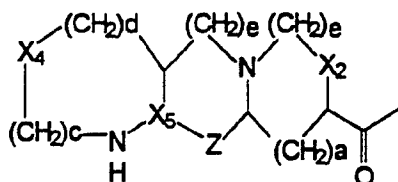


20

- 312 -

70. The compound according to claims 49 or 80, wherein R₁ is:

(v)



5

71. A pharmaceutical composition for treating or preventing an IL-1 mediated disease comprising a pharmaceutically effective amount of an ICE inhibitor according to any one of claims 1-70 and 80-124 and a pharmaceutically acceptable carrier.

72. A pharmaceutical composition for treating or preventing an autoimmune disease comprising a pharmaceutically effective amount of an ICE inhibitor according to any one of claims 1-70 and 80-124 and a pharmaceutically acceptable carrier.

73. A pharmaceutical composition for treating or preventing an inflammatory disease comprising a pharmaceutically effective amount of an ICE inhibitor according to any one of 1-70 and 80-124 and a pharmaceutically acceptable carrier.

74. A pharmaceutical composition for treating or preventing a neurodegenerative disease comprising a pharmaceutically effective amount of an ICE inhibitor according to any one of claims 1-70 and 80-124 and a pharmaceutically acceptable carrier.

- 313 -

75. A pharmaceutical composition for inhibiting an ICE-mediated function comprising a pharmaceutically effective amount of an ICE inhibitor according to any one of claims 1-70 and 80-124 and a pharmaceutically acceptable carrier.

76. A method for treating or preventing a disease selected from the group consisting of IL-1 mediated disease, autoimmune disease, inflammatory disease and neurodegenerative disease in a patient comprising the step of administering to said patient a pharmaceutical composition according to any one of claims 71 to 75.

77. A method for selecting an ICE inhibitor comprising the steps of:

a) selecting a candidate compound of defined chemical structure comprising at least two hydrogen bonding moieties, at least two moderately hydrophobic moieties and one electronegative moiety comprising one or more electronegative atoms attached either to the same atom or to adjacent atoms in the electronegative moiety;

b) determining a low-energy conformation for binding of said compound to the active site of ICE;

c) evaluating the capability of said compound in said conformation to form at least two hydrogen bonds with the non-carbon backbone atoms of Arg-341 and Ser-339 of ICE;

d) evaluating the capability of said compound in said conformation to associate with at least two of the binding pockets of ICE selected from the group consisting of the P2 binding pocket, the P3

- 314 -

binding pocket, the P4 binding pocket and the P' binding pocket;

5 e) evaluating the capability of said compound in said conformation to interact with the P1 binding pocket of ICE; and

f) accepting or rejecting said candidate compound as an ICE inhibitor based on the determinations and evaluations carried out in the preceeding steps.

10 78. The method of claim 77, additionally comprising the following steps which follow step e) and preceed step f):

g) evaluating the deformation energy of binding of said compound to ICE; and

15 h) evaluating the contribution of the sum of all electrostatic interactions between said compound and ICE when said compound is bound thereto in said conformation.

20 79. An ICE inhibitor selected by either of the methods according to claims 77 or 78.

80. A compound represented by the formula:



wherein:

X_1 is -CH;

30 g is 0 or 1;

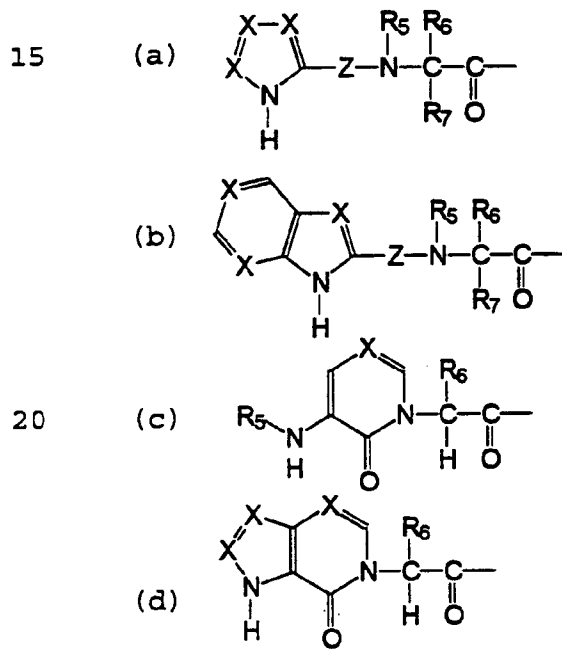
- 315 -

each J is independently selected from the group consisting of -H, -OH, and -F, provided that when a first and second J are bound to a C and said first J is -OH, said second J is -H;

5 m is 0, 1, or 2;

T is -OH, -CO-CO₂H, -CO₂H, or any bioisosteric replacement for -CO₂H;

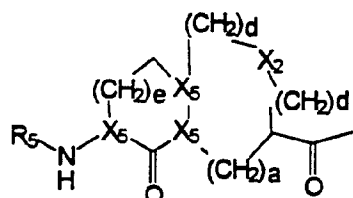
10 R₁ is selected from the group consisting of the following formulae, in which any ring may optionally be singly or multiply substituted at any carbon by Q₁, at any nitrogen by R₅, or at any atom by =O, -OH, -CO₂H, or halogen; any saturated ring may optionally be unsaturated at one or two bonds; and wherein R₁ (e) and R₁ (y) are optionally benzofused;



25

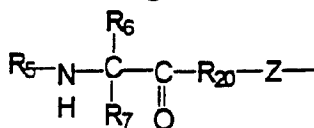
- 316 -

(e)



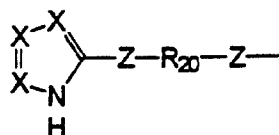
;

(f)



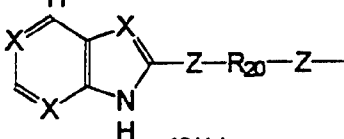
;

(g)



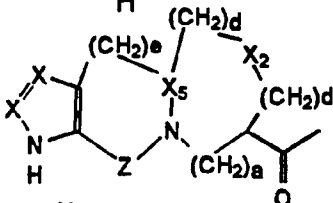
;

(h)



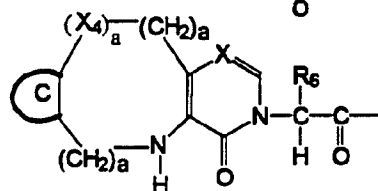
;

(i)



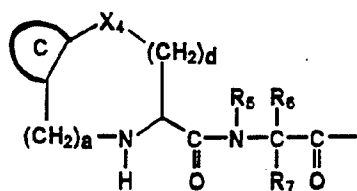
;

(j)



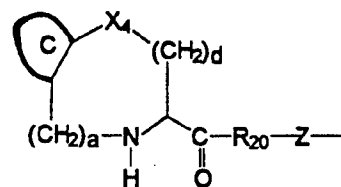
;

(k)



;

(l)

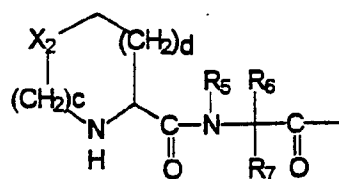


;

25

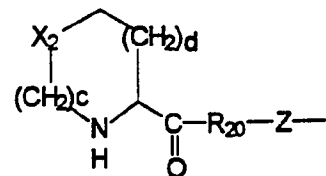
- 317 -

(m)



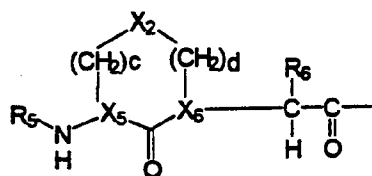
;

(n)



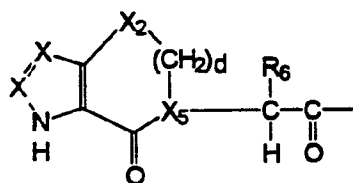
;

(o)



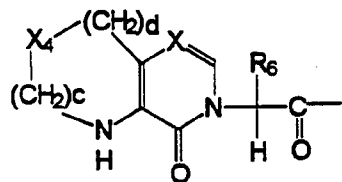
;

(p)



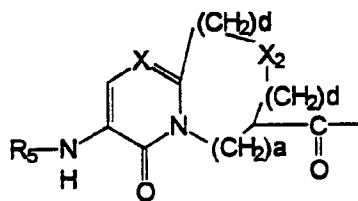
;

(q)



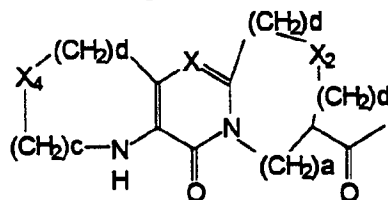
;

(r)



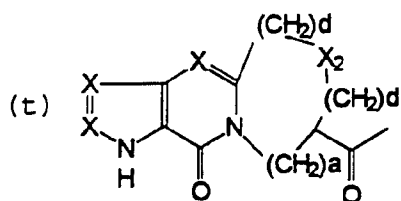
;

(s)

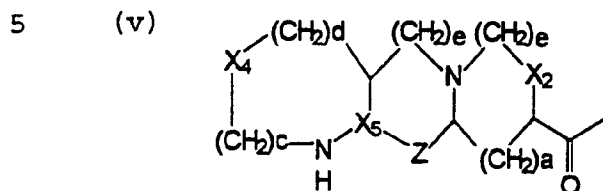


;

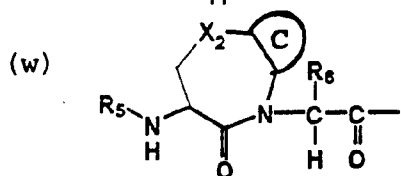
- 318 -



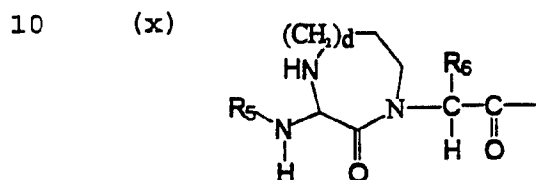
;



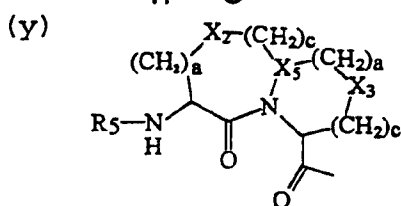
;



;

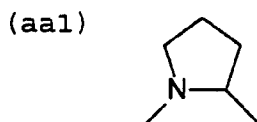


;

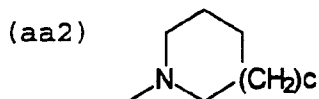


;

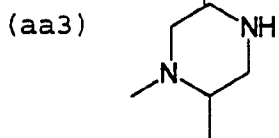
15 R_{20} is selected from the group consisting of:



;

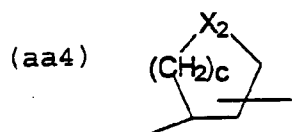


;

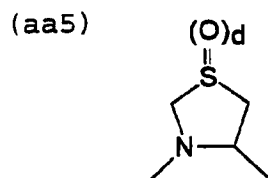


;

- 319 -

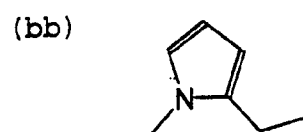


;



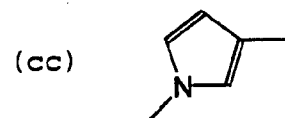
5

;

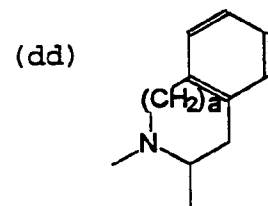


;

10

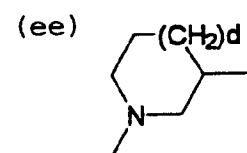


;



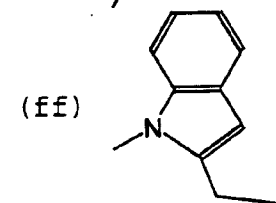
;

15

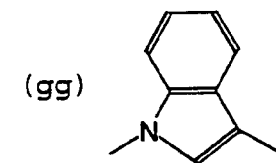


;

20

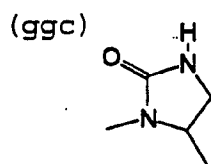
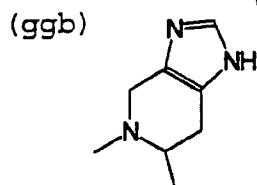
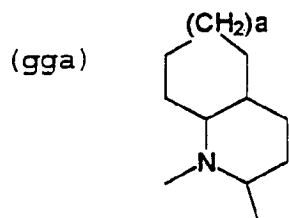


;



;

- 320 -



wherein each ring C is independently chosen from the group consisting of benzo, pyrido, thieno, pyrrolo, furano, thiazolo, isothiazolo, oxazolo, isoxazolo, pyrimido, imidazolo, cyclopentyl, and cyclohexyl;

R_3 is:

- CN,
- CH=CH- R_9 ,
- CH=N-O- R_9 ,
- $(CH_2)_{1-3}$ - T_1 - R_9 ,
- C J_2 - R_9 ,
- CO- R_{13} , or
- CO-CO-N $\begin{matrix} /R_5 \\ \backslash R_{10} \end{matrix}$;

each R_4 is independently selected from the group consisting of:

- H,
- Ar $_1$,

- 321 -

-R₉,
-T₁-R₉, and
-(CH₂)_{1,2,3}-T₁-R₉;

each T₁ is independently selected from the group

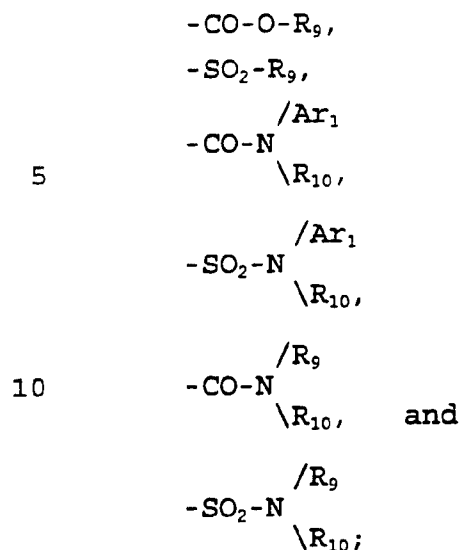
5 consisting of:

CH=CH-,
-O-,
-S-,
-SO-,
10 -SO₂-,
-NR₁₀-,
-NR₁₀-CO-,
-CO-,
-O-CO-,
15 -CO-O-,
-CO-NR₁₀-,
-O-CO-NR₁₀-,
-NR₁₀-CO-O-,
-NR₁₀-CO-NR₁₀-,
20 -SO₂-NR₁₀-,
-NR₁₀-SO₂-, and
-NR₁₀-SO₂-NR₁₀-;

each R₅ is independently selected from the group
consisting of:

25 -H,
-Ar₁,
-CO-Ar₁,
-SO₂-Ar₁,
-CO-NH₂,
30 -SO₂-NH₂,
-R₉,
-CO-R₉,

- 322 -



15 R_6 and R_7 taken together form a saturated 4-8 member carbocyclic ring or heterocyclic ring containing -O-, -S-, or -NH-; or R_7 is -H and R_6 is

-H

- Ar_1 ,

20 - R_9 ,

-(CH_2)_{1,2,3}- T_1 - R_9 , or

an α -amino acid side chain residue;

each R_9 is a C_{1-6} straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one or two Ar_1 groups;


25

each R_{10} is independently selected from the group consisting of -H or a C_{1-6} straight or branched alkyl group;

30 each R_{13} is independently selected from the group

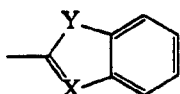
consisting of -Ar₂, -R₄ and -N-OH
 |
 R₅;

each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-, said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂, -CN,

=O, -OH, -perfluoro C₁₋₃ alkyl, , or -Q₁;

25 each Ar₂ is independently selected from the following group, in which any ring may optionally be singly or multiply substituted by -Q₁ and -Q₂:

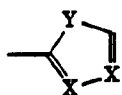
(hh)



i

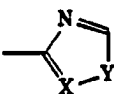
30

(ii)



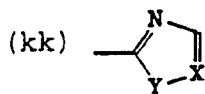
;

(jj)



; and

- 324 -



;

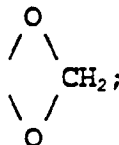
each Q_1 is independently selected from the group
 5 consisting of:

-Ar₁-O-Ar₁-R₉,-T₁-R₉,

and

10 - (CH₂)_{1,2,3}-T₁-R₉;

each Q_2 is independently selected from the group
 consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I,
 15 -NO₂, -CN, -CF₃, and



provided that when -Ar₁ is substituted with a Q_1
 20 group which comprises one or more additional -Ar₁
 groups, said additional -Ar₁ groups are not
 substituted with Q_1 ;

each X is independently selected from the group
 consisting of =N-, and =CH-;

25 each X_2 is independently selected from the group
 consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

each X_3 is independently selected from the group
 consisting of -CH₂-, -S-, -SO-, and -SO₂-;

each X_4 is independently selected from the group
 30 consisting of -CH₂- and -NH-;

- 325 -

each X_5 is independently selected from the group
consisting of $-\text{CH}-$ and $-\text{N}-$;

X_6 is $-\text{CH}-$ or $-\text{N}-$;

5 each Y is independently selected from the group
consisting of $-\text{O}-$, $-\text{S}-$, and $-\text{NH}$;

each Z is independently CO or SO_2 ;

each a is independently 0 or 1;

each c is independently 1 or 2;

10 each d is independently 0, 1, or 2; and

each e is independently 0, 1, 2, or 3;

provided that when

15 R_1 is (f),
 R_6 is an α -amino acid side chain residue, and
 R_7 is $-\text{H}$,
then (aa1) and (aa2) must be substituted with Q_1 ;

also provided that when

20 R_1 is (o),
 g is 0,
 J is $-\text{H}$,
 m is 1,
 R_6 is an α -amino acid side chain residue,
25 R_7 is $-\text{H}$,
 X_2 is $-\text{CH}_2-$,
 X_5 is $-\text{CH}-$,

- 326 -

X_6 is $-N-$, and
 $\quad \quad \quad |$

R_3 is $\begin{array}{c} /R_{10} \\ -CO-N \\ \backslash R_{10} \end{array}$, or $-CO-R_{13}$, when

R_{13} is:

$-CH_2-O-CO-Ar_1$,
 $-CH_2-S-CO-Ar_1$,
 $-CH_2-O-Ar_1$,
 $-CH_2-S-Ar_1$, or
 $-R_4$ when $-R_4$ is $-H$;

then the ring of the $R_1(o)$ group must be substituted with Q_1 or benzofused; and

provided that when

R_1 is (w),
 g is 0,
 J is $-H$,
 m is 1,

T is $-CO_2H$,
 X_2 is O ,
 R_5 is benzyloxycarbonyl, and
 ring C is benzo,

then R_3 cannot be $-CO-R_{13}$ when:

R_{13} is $-CH_2-O-Ar_1$ and

Ar_1 is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl wherein the phenyl is optionally substituted with a chlorine atom;

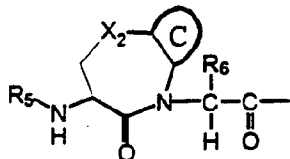
or when

R_{13} is $-CH_2-O-CO-Ar_1$, wherein
 Ar_1 is 2,6-dichlorophenyl.

- 327 -

81. The compound according to claim 80,
wherein R_1 is:

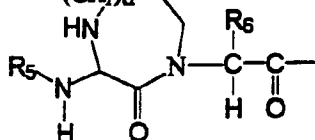
(w)



5

82. The compound according to claim 80,
wherein R_1 is:

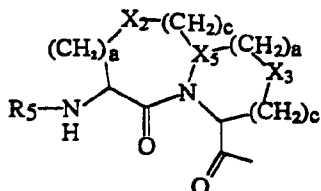
(x)



10

83. The compound according to claim 80,
wherein R_1 is:

(y)



15

84. The compound according to claim 80,
wherein:

X_1 is -CH;

g is 0;

20

J is -H;

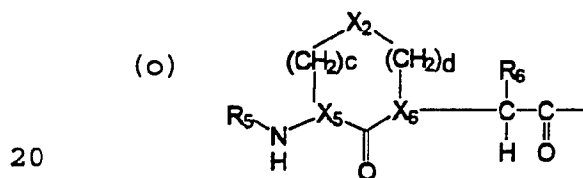
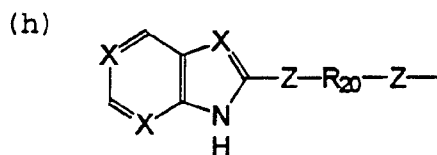
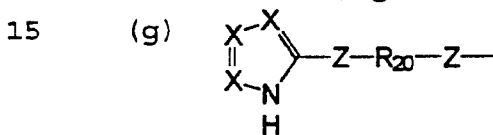
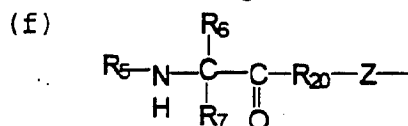
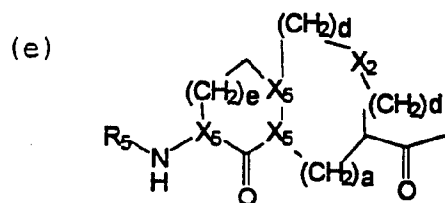
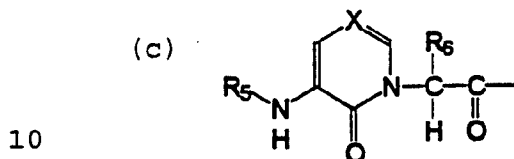
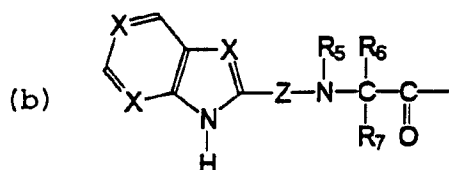
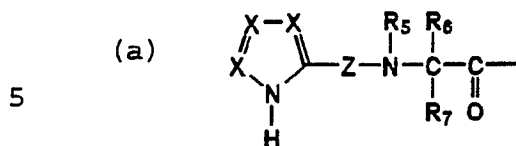
m is 0 or 1 and T is -CO-CO₂H, or any bioisosteric
replacement for -CO₂H, or

m is 1 and T is -CO₂H;

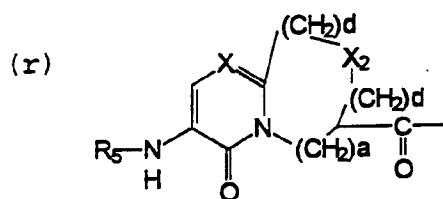
R_1 is selected from the group consisting of the
following formulae, in which any ring may optionally
be singly or multiply substituted at any carbon by

25

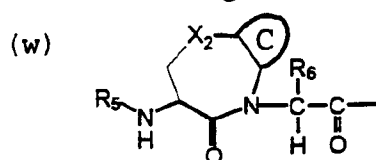
Q₁, at any nitrogen by R₅, or at any atom by =O, -OH, -CO₂H, or halogen, and wherein (e) is optionally benzofused:



- 329 -

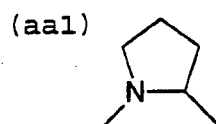


, or

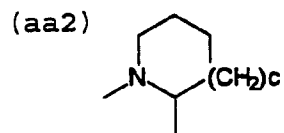


;

5

R₂₀ is:

, or



10

and c is 1;

ring C is benzo optionally substituted with
-C₁₋₃ alkyl, -O-C₁₋₃ alkyl, -Cl, -F or -CF₃;

when R₁ is (a) or (b), R₅ is preferably -H, and

15

when R₁ is (c), (e), (f), (o), (r), (w), (x) or
(y), R₅ is preferably:

-CO-Ar₁-SO₂-Ar₁,-CO-NH₂,-CO-NH-Ar₁-CO-R₉,-CO-O-R₉,

20

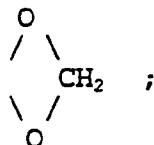
- 330 -

-SO₂-R₉, or-CO-NH-R₉,R₇ is -H and R₆ is: -H,-R₉, or5 -Ar₁;

R₉ is a C₁₋₆ straight or branched alkyl group optionally substituted with =O and optionally substituted with -Ar₁;

10 R₁₀ is -H or a -C₁₋₃ straight or branched alkyl group;

Ar₁ is phenyl, naphthyl, pyridyl, benzothiazolyl, thienyl, benzothienyl, benzoxazolyl, 2-indanyl, or indolyl substituted with -O-C₁₋₃ alkyl, -NH-C₁₋₃ alkyl, -N-(C₁₋₃ alkyl)₂, -Cl, -F, -CF₃,
15 -C₁₋₃ alkyl, or



20 Q₁ is R₉ or -(CH₂)_{0,1,2}-T₁-(CH₂)_{0,1,2}-Ar₁, wherein T₁ is -O- or -S-;

each X is independently selected from the group consisting of =N-, and =CH-;

25 each X₂ is independently selected from the group consisting of -O-, -CH₂-, -NH-, -S-, -SO-, and -SO₂-;

each X₃ is independently selected from the group consisting of -CH- and -N-;



- 331 -

X_6 is $\begin{array}{c} -CH- \\ | \end{array}$ or $\begin{array}{c} -N- \\ | \end{array}$,

provided that when:

R_1 is $R_1(o)$,

5 X_2 is $-CH_2-$,

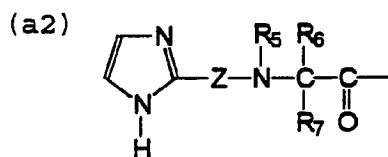
X_5 is $\begin{array}{c} -CH- \\ | \end{array}$, and

10 X_6 is $\begin{array}{c} -N- \\ | \end{array}$,

then the ring of the $R_1(o)$ group must be substituted with Q_1 or benzofused; and

Z is $C=O$.

15 85. The compound according to claim 84, wherein the R_1 group is



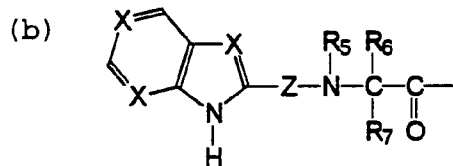
optionally substituted with Q_1 , wherein

R_5 is $-H$;

20 R_7 is $-H$; and

Z is $C=O$.

86. The compound according to claim 84, wherein the R_1 group is



optionally substituted with Q_1 , wherein

- 332 -

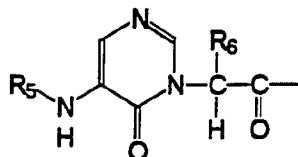
R_5 is -H;

R_7 is -H; and

Z is C=O.

87. The compound according to claim 84,
5 wherein the R_1 group is

(c1)



which is optionally substituted with Q_1 ;

10

provided that when R_1 is (c1),

g is 0,

J is -H,

m is 1,

15

T is -CO₂H,

X is N,

R_5 is benzyloxycarbonyl, and

R_6 is -H,

then R_3 cannot be -CO- R_{13} when

20

R_{13} is -CH₂-O-Ar₁ and

Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-5-yl, wherein the phenyl is optionally substituted with a chlorine atom; or when

25

R_{13} is -CH₂-O-CO-Ar₁, wherein

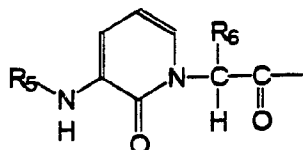
Ar₁ is 2,6-dichlorophenyl,

and when the 2-position of the scaffold ring is substituted with para-fluoro-phenyl.

- 333 -

88. The compound according to claim 84,
wherein the R_1 group is:

(c2)

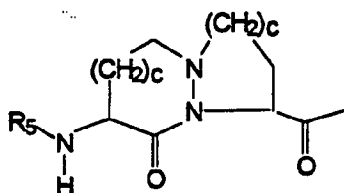


5

which is optionally substituted with Q_1 .

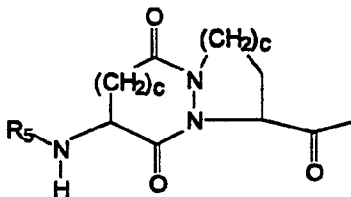
89. The compound according to claim 84,
wherein the R_1 group is:

(e1)



10

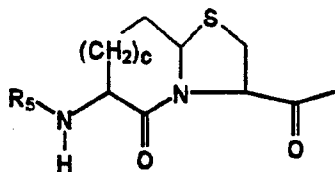
(e2)



, or

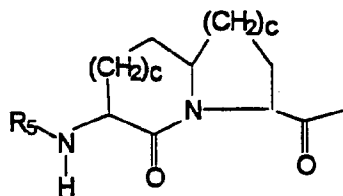
and c is 2; or

(e4)



15

(e7)



, or

which is optionally benzofused,
and c is 1 or 2;

provided that when R_1 is (e4),

- 334 -

g is 0,
J is -H,
m is 1,
T is -CO₂H,
5 R₅ is benzyloxycarbonyl, and
c is 1,

then R₃ cannot be -CO-R₁₃ when
R₁₃ is -CH₂-O-Ar₁ and
Ar₁ is 1-phenyl-3-trifluoromethyl-pyrazole-
10 5-yl, wherein the phenyl is optionally substituted
with a chlorine atom; or when

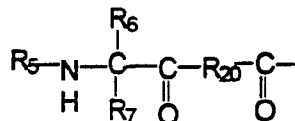
R₁₃ is -CH₂-O-CO-Ar₁, wherein
Ar₁ is 2,6-dichlorophenyl,
15 and when the 2-position of the scaffold ring is
substituted with para-fluoro-phenyl; and

also provided that when
R₁ is (e7),
g is 0,
20 J is -H,
m is 1,
T is -CO₂H or -CO-NH-OH,
R₅ is a protective group for the N atom of an
amino acid side chain residue, and
25 each c is 1,

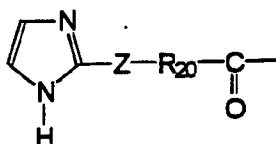
then R₃ cannot be -CO-R₁₃ when
R₁₃ is:
-CH₂-O-CO-Ar₁,
-CH₂-S-CO-Ar₁,
30 -CH₂-O-Ar₁, or
-CH₂-S-Ar₁.

- 335 -

90. The compound according to claim 84,
wherein the R_1 group is
(f1)



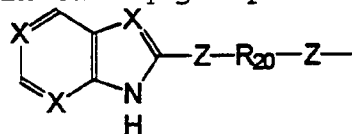
5 91. The compound according to claim 84,
wherein the R_1 group is
(g2)



, wherein
 R_{20} is (aa1) optionally substituted singly or
10 multiply with Q_1 ; and

Z is C=O.

92. The compound according to claim 84,
wherein the R_1 group is
(h)



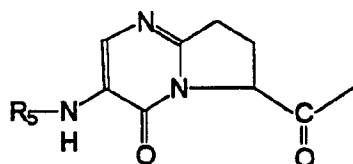
15 , wherein

R_{20} is (aa1) optionally substituted singly or
multiply with Q_1 ; and

Z is C=O.

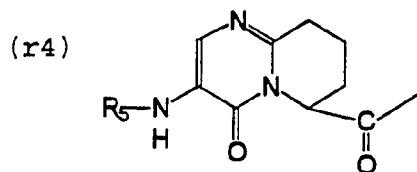
93. The compound according to claim 84,
20 wherein the R_1 group is:

(r3)

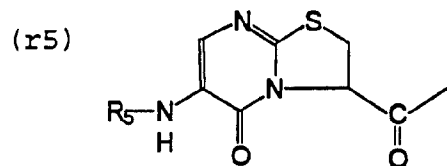


;

- 336 -



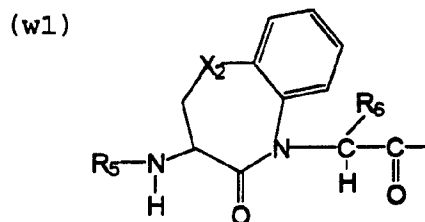
;



; and

optionally substituted with Q₁.

5 94. The compound according to claim 84,
wherein the R₁ group is



; wherein

X₂ is:

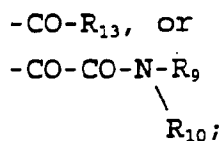
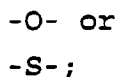
10 -O- ,
 -S- ,
 -SO₂-, or
 -NH-;

15 optionally substituted with R₅ or Q₁ at X₂ when X₂
is -NH-; and

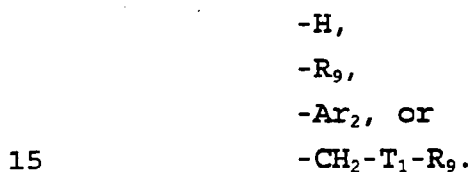
 ring C is benzo substituted with -C₁₋₃ alkyl,
-O-C₁₋₃ alkyl, -Cl, -F or -CF₃.

20 95. The compound according to claim 84,
wherein
 R₃ is:

- 337 -

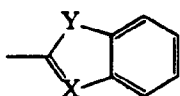
5 T_1 is:

10 R_9 is a C_{1-6} straight or branched alkyl group optionally substituted with =O and optionally substituted with Ar_1 ; and

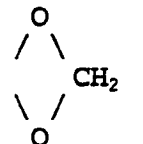
 R_{13} is:

96. The compound according to claim 95, wherein $-\text{Ar}_2$ is:

(hh)



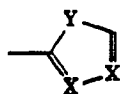
20 optionally substituted singly or multiply with $-\text{C}_{1-6}$ alkyl, $-\text{O}-\text{C}_{1-6}$ alkyl, $-\text{NH}-\text{C}_{1-6}$ alkyl, $-\text{N}-(\text{C}_{1-6} \text{ alkyl})_2$, $-\text{S}-\text{C}_{1-6}$ alkyl, $-\text{Cl}$, $-\text{F}$, $-\text{CF}_3$, or



25

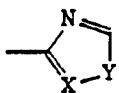
97. The compound according to claim 95, wherein $-\text{Ar}_2$ is:

(ii)



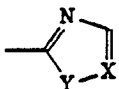
- 338 -

(jj)



, or

(kk)



5

98. The compound according to claim 95,
wherein:

R_{13} is $-\text{CH}_2-\text{O}-R_9$; wherein:

10 R_9 is a C_{1-6} straight or branched alkyl group
optionally substituted with $=\text{O}$ and optionally
substituted with Ar_1 .

99. The compound according to claim 95,
wherein:

R_{13} is $-\text{CH}_2-\text{S}-R_9$; wherein:

15 R_9 is a C_{1-6} straight or branched alkyl group
optionally substituted with Ar_1 .

100. The compound according to claim 98,
wherein:

R_{13} is $-\text{CH}_2-\text{O}-R_9$; wherein:

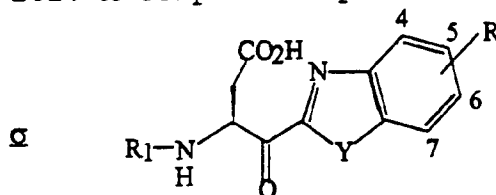
20 R_9 is a C_{1-6} straight or branched alkyl group
optionally substituted with Ar_1 .

101. The compound according to claim 95,
wherein:

R_{13} is H.

- 339 -

102. A compound represented by the formula:



wherein the ring is optionally substituted with
one or more R groups, preferably 0, 1 or 2; and
wherein:

R_1 is $R_5-(A)_p$;

R_5 is selected from the group consisting of:

-H,

-Ar₁,

10 -CO-Ar₁,

-SO₂-Ar₁,

-R₉,

-CO-R₉,

-CO-O-R₉,

15 -SO₂-R₉,

/Ar₁

-CO-N
 \R₁₀,

20 -SO₂-N
 \R₁₀,

/R₉

25 -CO-N
 \R₁₀, and

/R₉
-SO₂-N
 \R₁₀;

30 each A is independently selected from the group
consisting of any α -amino acid;

- 340 -

p is 0, 1, 2, 3 or 4;

Y is

5 -O-,
 -S- or
 -NH; and

R is:

10 -H,
 -O-C₁₋₆ alkyl,
 -NH(C₁₋₆ alkyl),
 -N(C₁₋₆ alkyl)₂,
 -S-C₁₋₆ alkyl,
 -C₁₋₆ alkyl, or
 -Q₂;

15 each R₉ is a C₁₋₆ straight or branched alkyl group
optionally singly or multiply substituted by -OH, -F,
or =O and optionally substituted with one Ar₁ group;

 each R₁₀ is independently selected from the group
consisting of -H or a C₁₋₆ straight or branched alkyl
group;

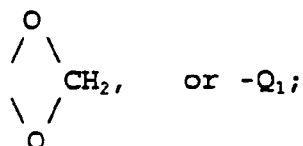
20 each T₁ is independently selected from the group
consisting of:

 -CH=CH-,
 -O-,
 -S-,
25 -SO-,
 -SO₂-,
 -NR₁₀-,
 -NR₁₀-CO-,
 -CO-,
30 -O-CO-,

- 341 -

-CO-O-,
 -CO-NR₁₀-,
 -O-CO-NR₁₀-,
 -NR₁₀-CO-O-,
 5 -NR₁₀-CO-NR₁₀-,
 -SO₂-NR₁₀-,
 -NR₁₀-SO₂-, and
 -NR₁₀-SO₂-NR₁₀-,

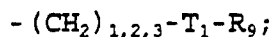
each Ar₁ is a cyclic group independently selected
 10 from the set consisting of an aryl group which
 contains 6, 10, 12, or 14 carbon atoms and between 1
 and 3 rings, a cycloalkyl group which contains
 between 3 and 15 carbon atoms and between 1 and 3
 rings, said cycloalkyl group being optionally
 15 benzofused, and a heterocycle group containing
 between 5 and 15 ring atoms and between 1 and 3
 rings, said heterocycle group containing at least one
 heteroatom group selected from -O-, -S-, -SO-, -SO₂-,
 =N-, and -NH-, said heterocycle group optionally
 20 containing one or more double bonds, said heterocycle
 group optionally comprising one or more aromatic
 rings, and said cyclic group optionally being singly
 or multiply substituted by -NH₂, -CO₂H, -Cl, -F, -Br,
 -I, -NO₂, -CN, =O, -OH,
 25 -perfluoro C₁₋₃ alkyl,



30 each Q₁ is independently selected from the group
 consisting of:

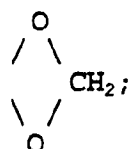
-Ar₁
 -R₉,
 -T₁-R₉, and

- 342 -



each Q_2 is independently selected from the group consisting of $-\text{OH}$, $-\text{NH}_2$, $-\text{CO}_2\text{H}$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{I}$, $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, and

5

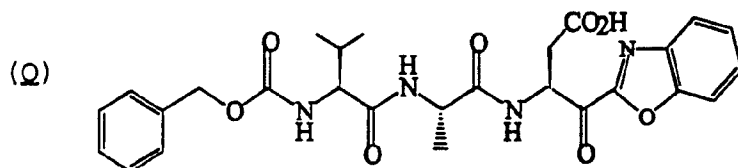


provided that when $-\text{Ar}_1$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_1$ groups, said additional $-\text{Ar}_1$ groups are not substituted with Q_1 .

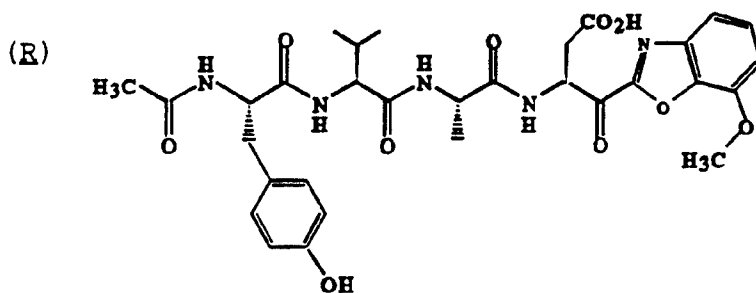
10

103. A compound according to claim 102 selected from the group consisting of:

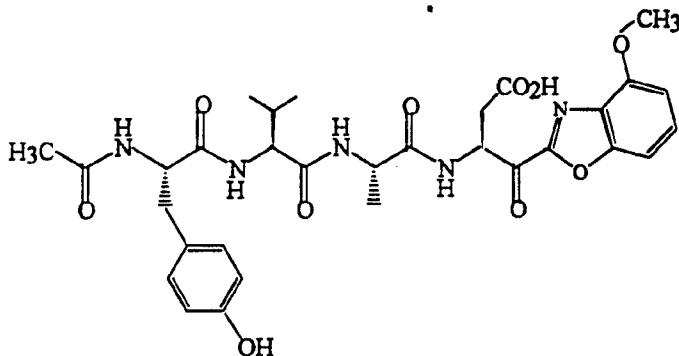
15



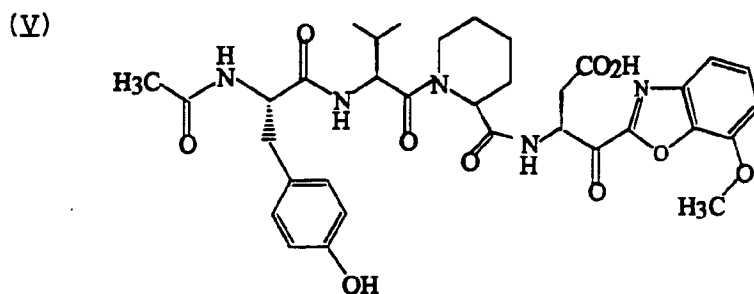
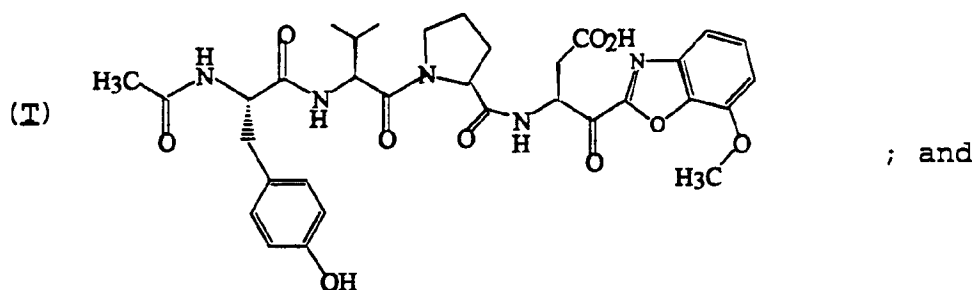
20



(S)



- 343 -



5

104. A compound according to claim 102 wherein each A is independently selected from the group consisting of the α -amino acids:

- alanine,
 histidine,
 lysine,
 phenylalanine,
 proline,
 tyrosine,
 valine,
 leucine,
 isoleucine,
 glutamine,
 methionine,
 homoproline,
 3-(2-thienyl) alanine, and
 3-(3-thienyl) alanine.

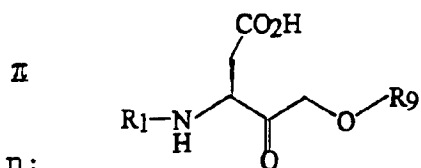
10

15

20

- 344 -

105. A compound represented by the formula:



wherein:

5 R_1 is $\text{R}_5\text{-(A)}_p\text{-}$;

each T_1 is independently selected from the group consisting of:

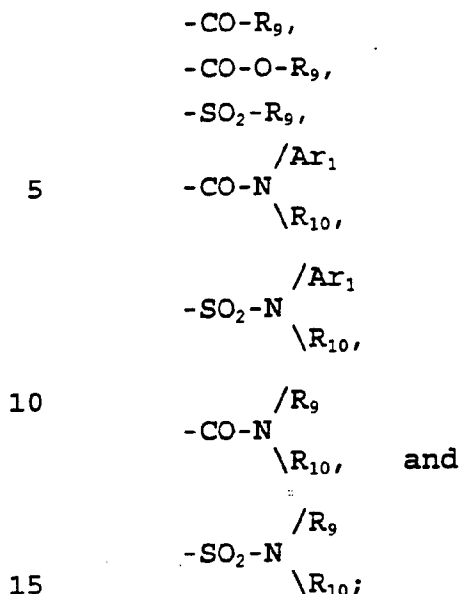
10 -CH=CH- ,
 -O- ,
 -S- ,
 -SO- ,
 $\text{-SO}_2\text{-}$,
 $\text{-NR}_{10}\text{-}$,
 $\text{-NR}_{10}\text{-CO-}$,
15 -CO- ,
 -O-CO- ,
 -CO-O- ,
 $\text{-CO-NR}_{10}\text{-}$,
 $\text{-O-CO-NR}_{10}\text{-}$,
20 $\text{-NR}_{10}\text{-CO-O-}$,
 $\text{-NR}_{10}\text{-CO-NR}_{10}\text{-}$,
 $\text{-SO}_2\text{-NR}_{10}\text{-}$,
 $\text{-NR}_{10}\text{-SO}_2\text{-}$, and
 $\text{-NR}_{10}\text{-SO}_2\text{-NR}_{10}\text{-}$;

25

R_5 is selected from the group consisting of:

-H ,
 -Ar_1 ,
 -CO-Ar_1 ,
30 $\text{-SO}_2\text{-Ar}_1$,
 -R_9 ,

- 345 -



each A is independently selected from the group consisting of any α -amino acid;

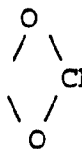
p is 0, 1, 2, 3 or 4;

each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with an Ar₁ group;

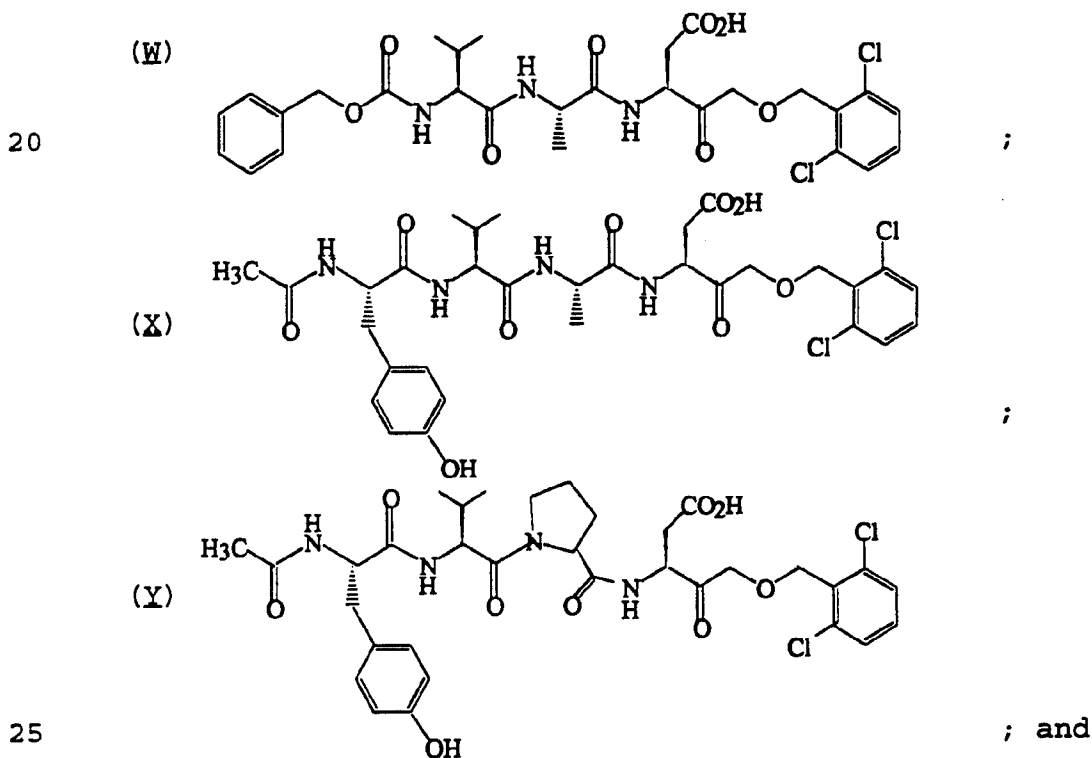
each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3 rings, said cycloalkyl group being optionally benzofused, and a

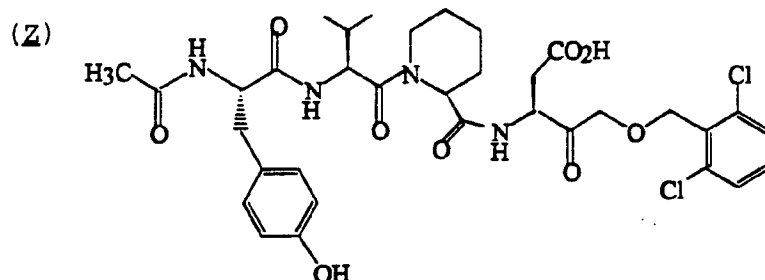
- 346 -

- heterocycle group containing between 5 and 15 ring atoms and between 1 and 3 rings, said heterocycle group containing at least one heteroatom group selected from -O-, -S-, -SO-, -SO₂-, =N-, and -NH-,
- 5 said heterocycle group optionally containing one or more double bonds, said heterocycle group optionally comprising one or more aromatic rings, and said cyclic group optionally being singly or multiply substituted by -NH₂, -CO₂H, -Cl, -F, -Br, -I, -NO₂,
- 10 -CH, =O, -OH, -perfluoro C₁₋₃ alkyl, , -R₉, or
- 15 -T₁-R₉.

106. A compound according to claim 105 selected from the group consisting of:



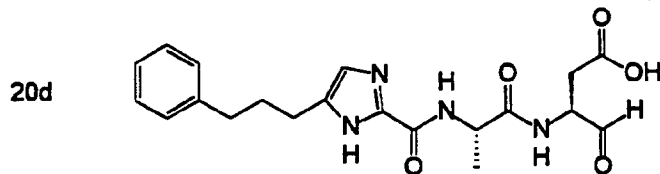
- 347 -



107. A compound according to claim 105
 wherein each A is independently selected from the
 group consisting of the α -amino acids:

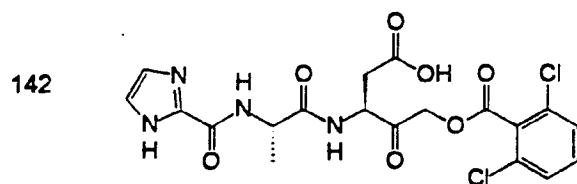
alanine,
 histidine,
 lysine,
 phenylalanine,
 proline,
 tyrosine,
 valine,
 leucine,
 isoleucine,
 glutamine,
 methionine,
 homoproline,
 3-(2-thienyl) alanine, and
 3-(3-thienyl) alanine.

108. The compound according to claim 85,
 selected from the group consisting of:



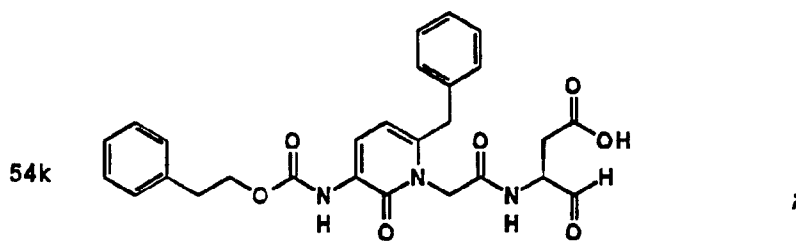
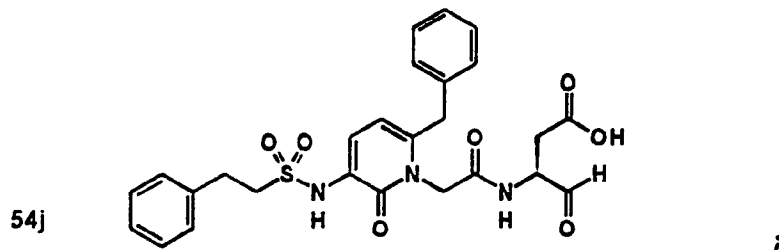
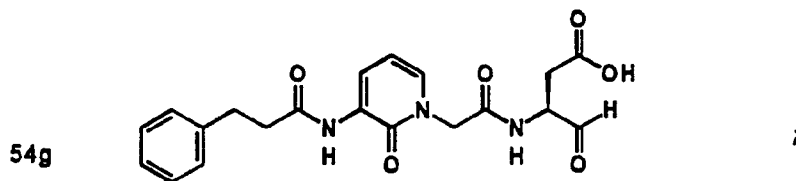
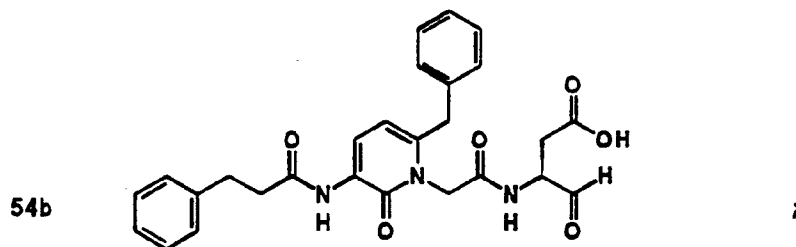
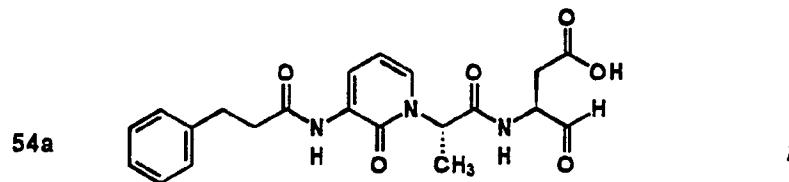
; and

- 348 -

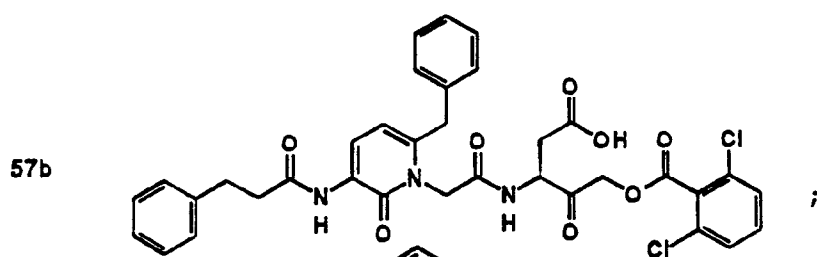


5

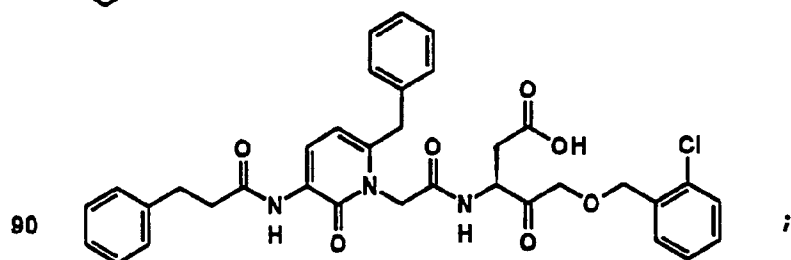
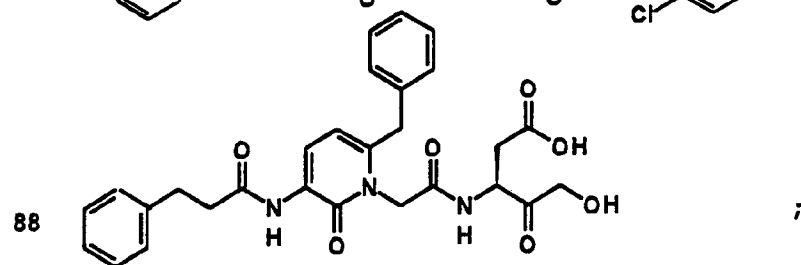
109. The compound according to claim 88,
selected from the group consisting of



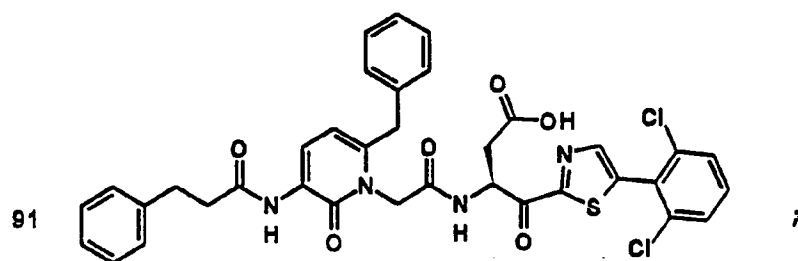
- 349 -



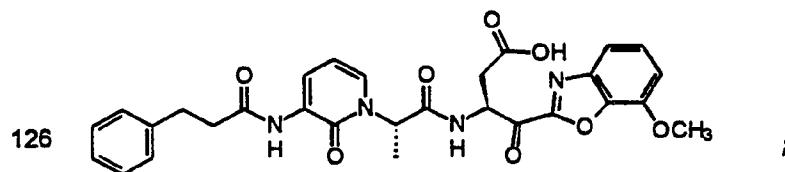
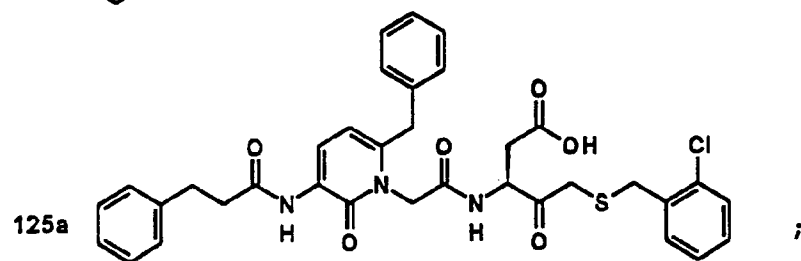
5



10

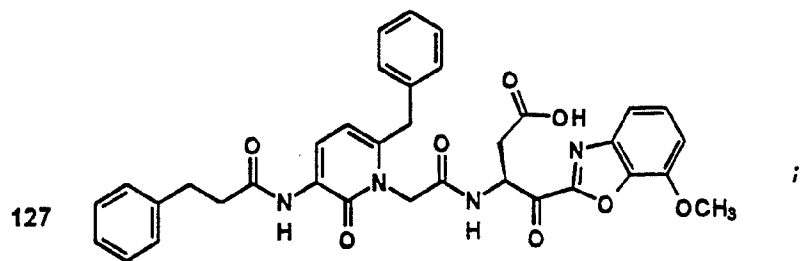


15

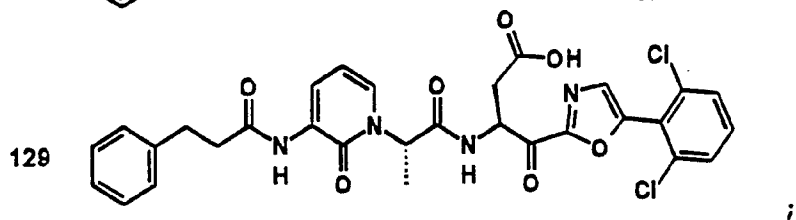
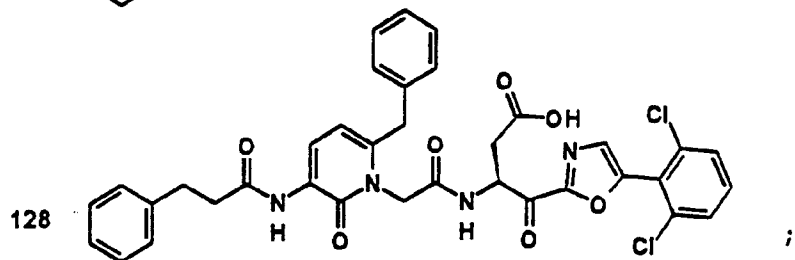


- 350 -

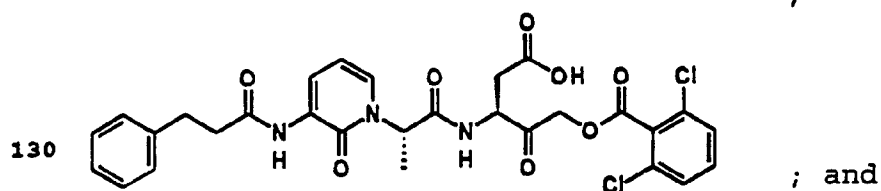
5



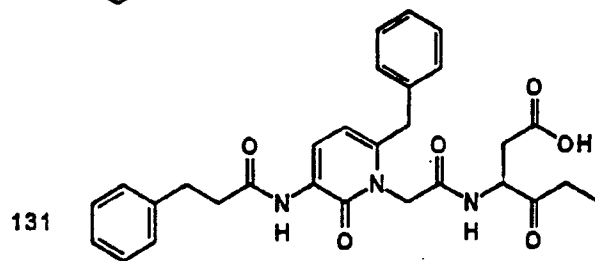
10



15



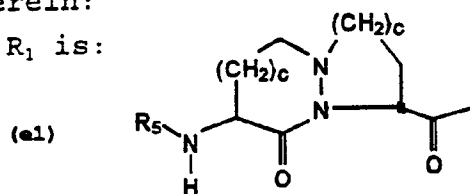
20



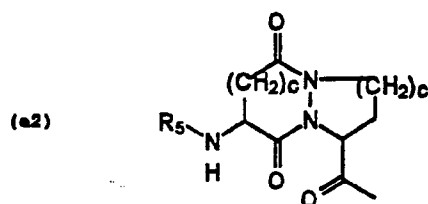
- 351 -

110. The compound according to claim 89,
wherein:

R_1 is:



, or



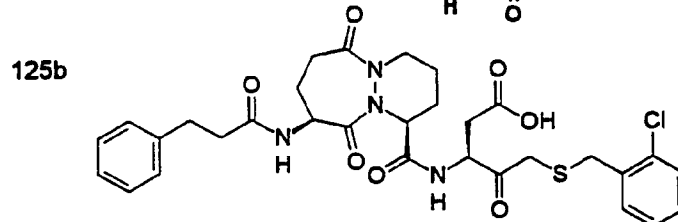
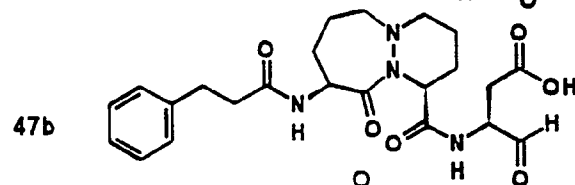
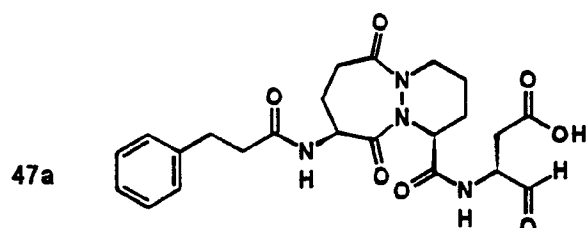
and c is 2;

m is 1;

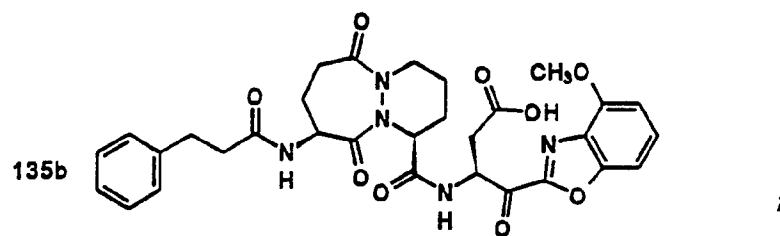
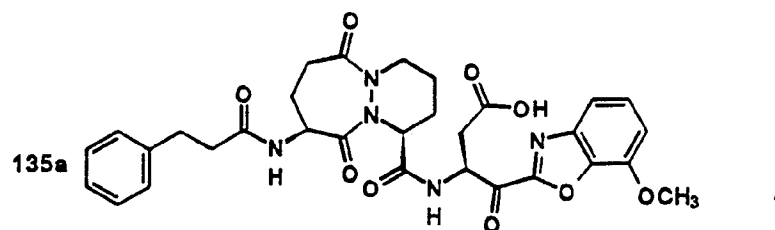
T is $-\text{CO}_2\text{H}$; and

R_3 is $-\text{CO}-R_{13}$.

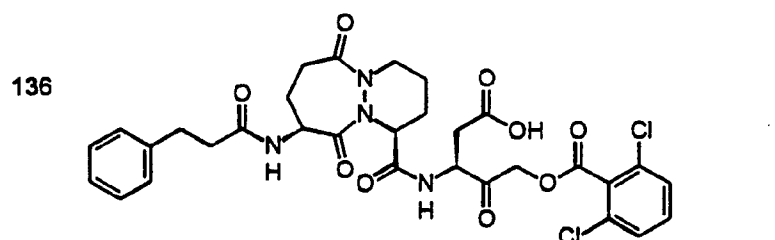
111. The compound according to claim 110,
selected from the group consisting of:



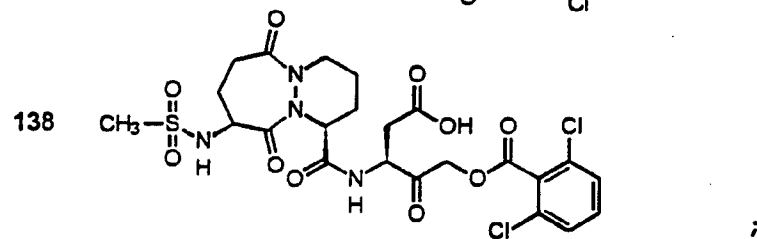
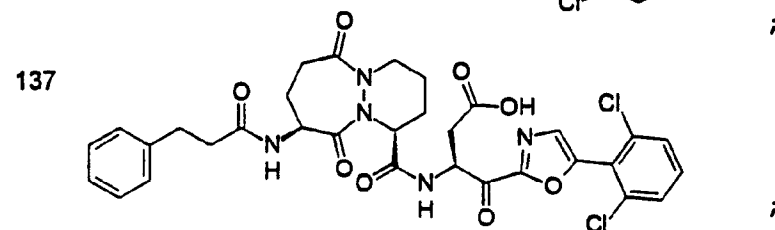
- 352 -



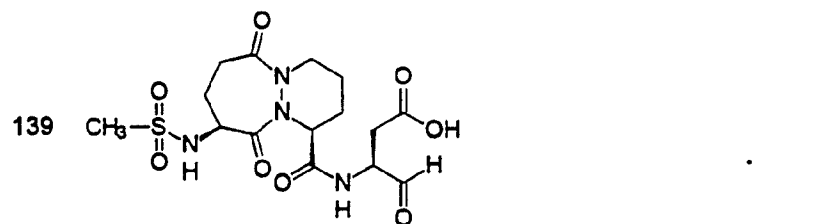
5



10



15

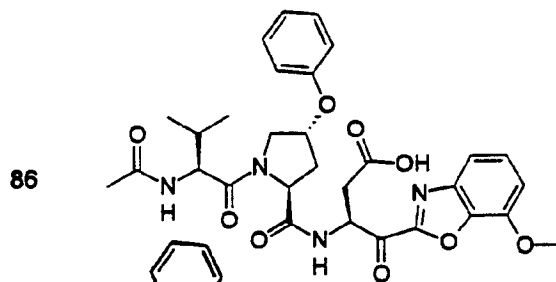


20

- 353 -

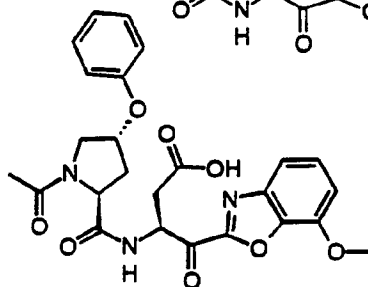
112. The compound according to claim 90,
selected from the group consisting of:

5



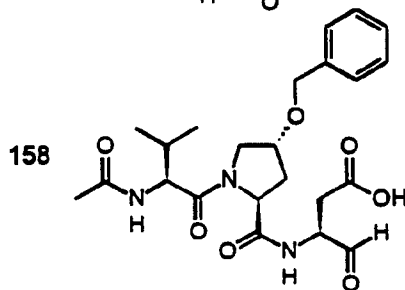
;

87



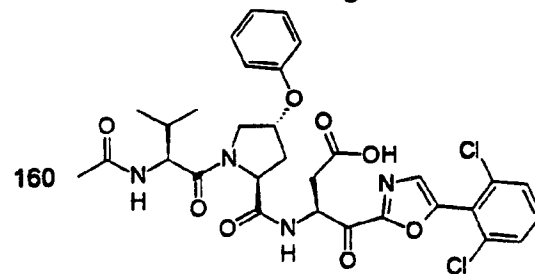
;

10



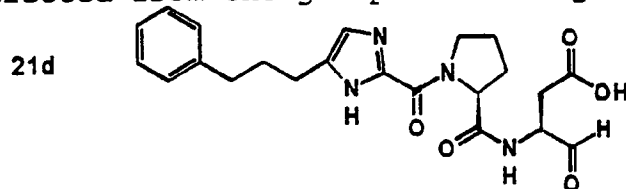
; and

15



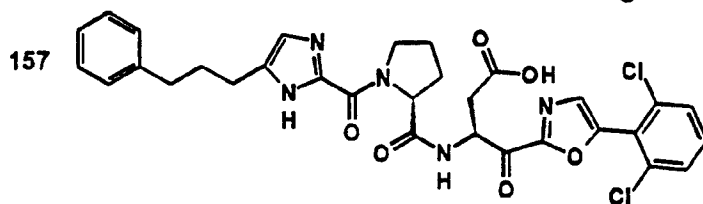
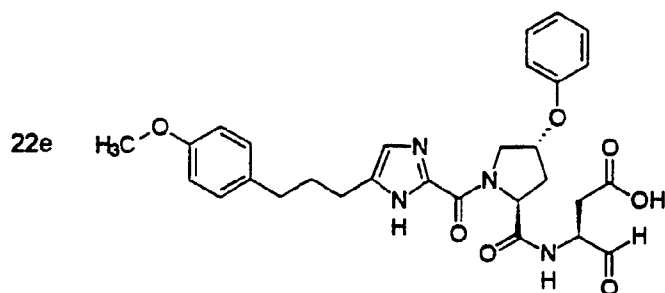
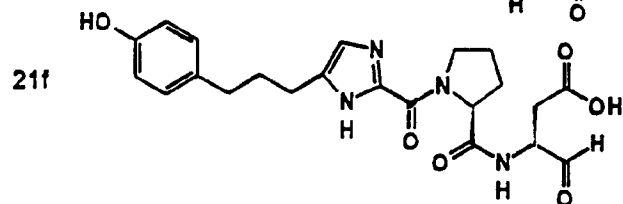
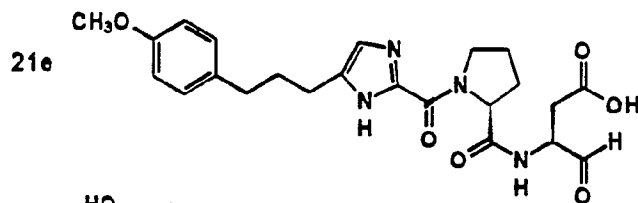
113. The compound according to claim 91,
selected from the group consisting of:

20



;

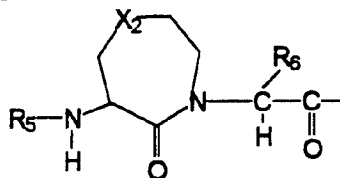
- 354 -



114. The compound according to claim 84,
wherein:

R_1 is:

(o6)



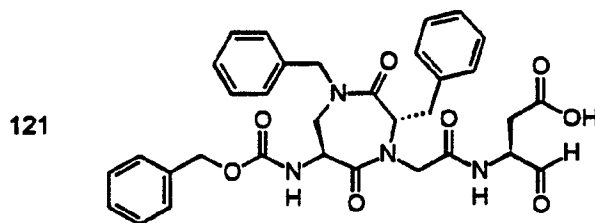
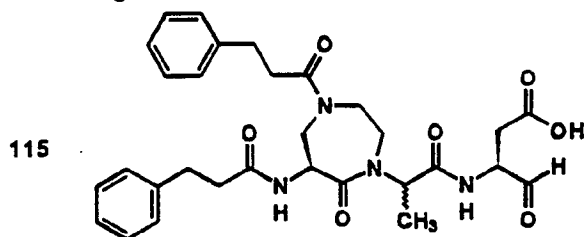
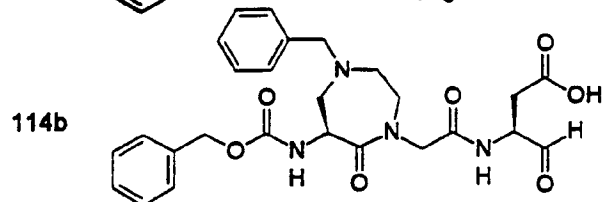
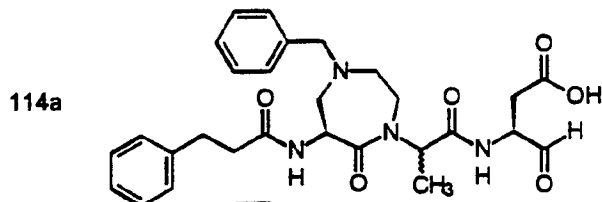
X_2 is -NH-;

m is 1;

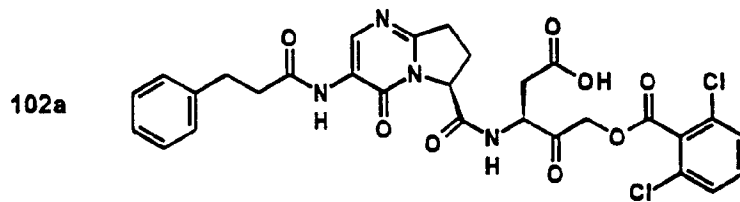
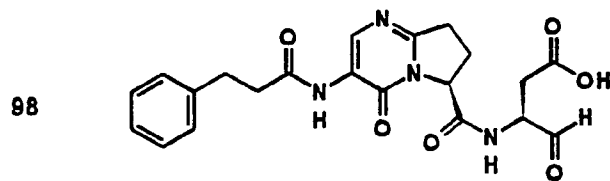
T is -CO₂H;

R_3 is -CO-R₁₃.

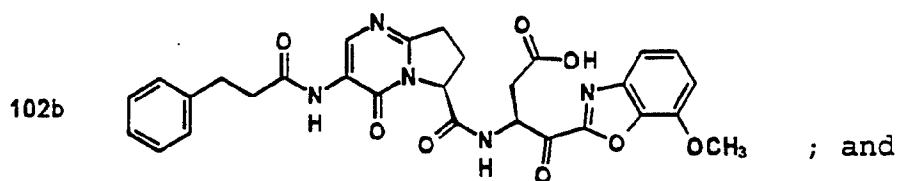
115. The compound according to claim 114,
selected from the group consisting of:



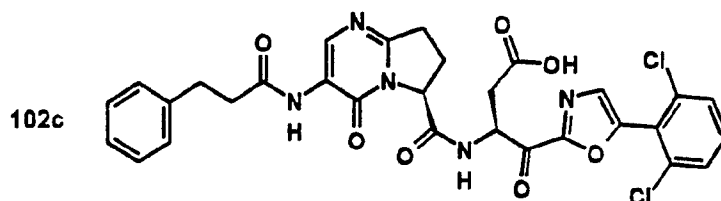
116. The compound according to claim 93,
selected from the group consisting of:



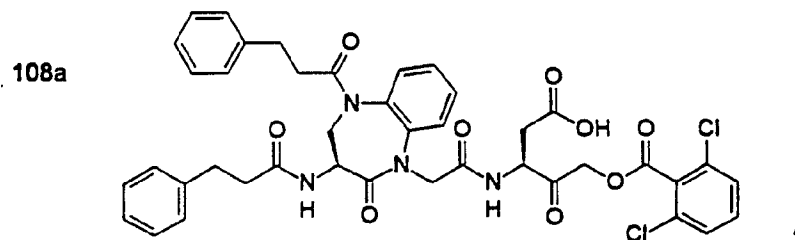
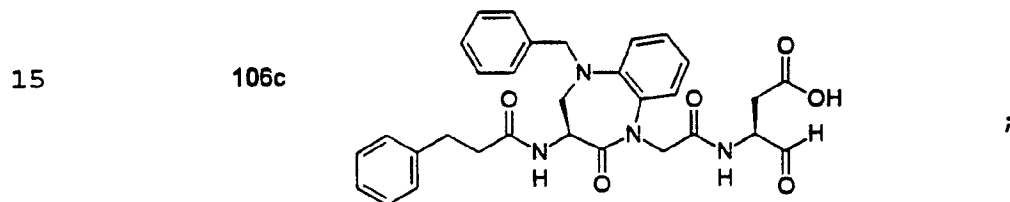
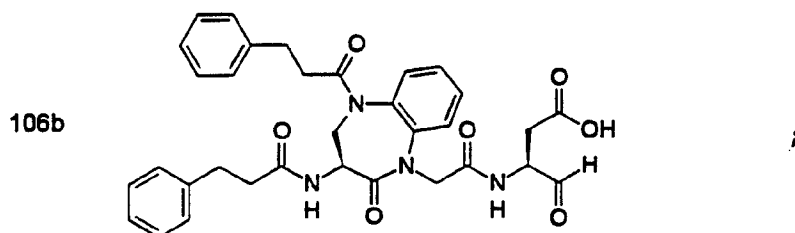
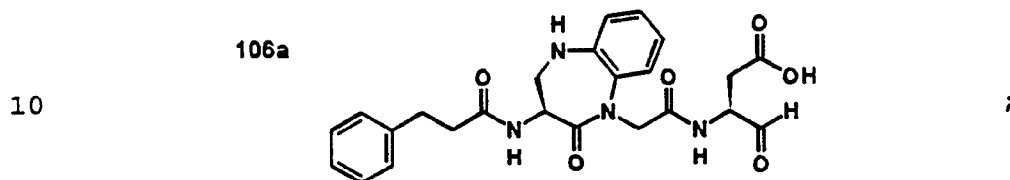
- 356 -



5

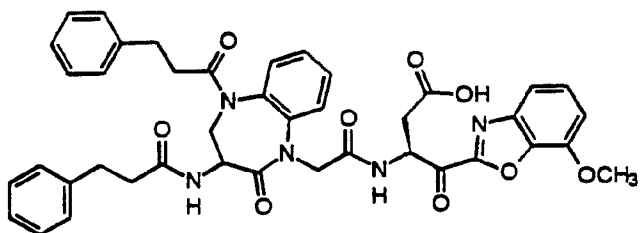


117. The compound according to claim 94,
selected from the group consisting of:



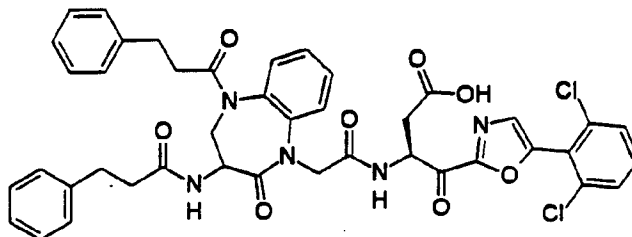
- 357 -

108b

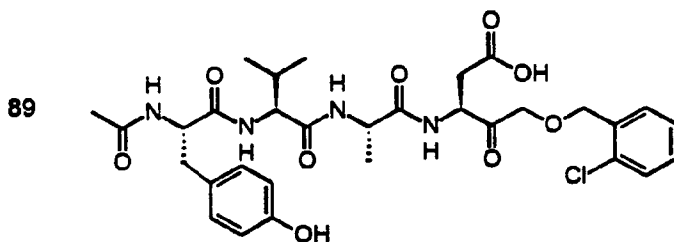


; and

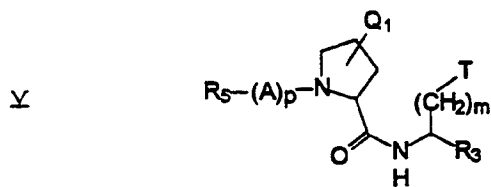
108c



118. The compound according to claim 105:



119. A compound represented by the formula:



wherein:

m is 0, 1, or 2

T is -CO₂H, or any bioisosteric replacement for -CO₂H

- 358 -

R_3 is

-CN,

-CO- R_{13} , or

5 -CO-CO-N $\begin{matrix} /R_5 \\ \backslash R_{10} \end{matrix}$;

R_5 is selected from the group consisting of:

-H,

-Ar₁,

10 -CO-Ar₁,

-SO₂-Ar₁,

-R₉,

-CO-R₉,

-CO-O-R₉,

15 -SO₂-R₉,

-CO-N $\begin{matrix} /Ar_1 \\ \backslash R_{10} \end{matrix}$,

20 -SO₂-N $\begin{matrix} /Ar_1 \\ \backslash R_{10} \end{matrix}$,

-CO-N $\begin{matrix} /R_9 \\ \backslash R_{10} \end{matrix}$, and

25 -SO₂-N $\begin{matrix} /R_9 \\ \backslash R_{10} \end{matrix}$;

30 each A is independently selected from the group
consisting of any α -amino acid;

p is 2 or 3;

each R₉ is a C₁₋₆ straight or branched alkyl group
optionally singly or multiply substituted by -OH, -F,

- 359 -

or =O and optionally substituted with one Ar₁ group;

each T₁ is independently selected from the group consisting of:

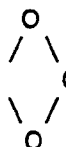
- CH=CH-,
- 5 -O-,
- S-,
- SO-,
- SO₂-,
- NR₁₀-,
- 10 -NR₁₀-CO-,
- CO-,
- O-CO-,
- CO-O-,
- CO-NR₁₀-,
- 15 -O-CO-NR₁₀-,
- NR₁₀-CO-O-,
- NR₁₀-CO-NR₁₀-,
- SO₂-NR₁₀-,
- NR₁₀-SO₂-, and
- 20 -NR₁₀-SO₂-NR₁₀-;

each R₁₀ is independently selected from the group consisting of -H or a -C₁₋₆ straight or branched alkyl group;

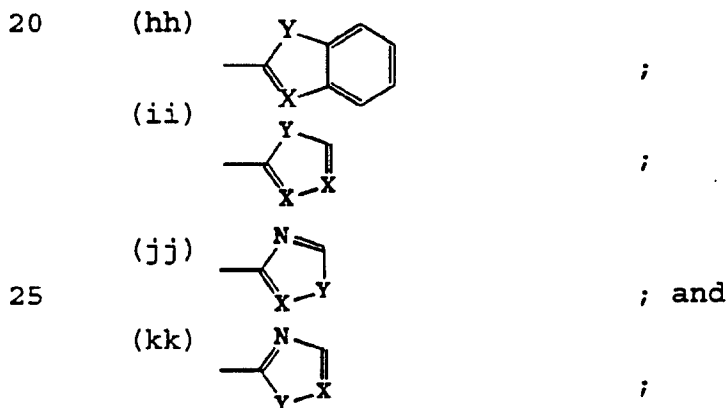
- 25 each R₁₃ is independently selected from the group consisting of H, R₉, Ar₂, and -CH₂-T₁-R₉;

- 30 each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3

- 360 -

rings, said cycloalkyl group being optionally
 benzofused, and a heterocycle group containing
 between 5 and 15 ring atoms and between 1 and 3
 rings, said heterocycle group containing at least one
 5 heteroatom group selected from -O-, -S-, -SO-, -SO₂-,
 =N-, and -NH-, said heterocycle group optionally
 containing one or more double bonds, said heterocycle
 group optionally comprising one or more aromatic
 rings, and said cyclic group optionally being singly
 10 or multiply substituted by -NH₂, -CO₂H,
 -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH,
 -perfluoro C₁₋₃ alkyl, , or -Q₁; and
 15

each Ar₂ is independently selected from the
 following group, in which any ring may optionally be
 singly or multiply substituted by -Q₁ and -Q₂:



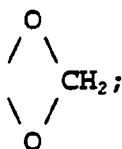
each Q₁ is independently selected from the group
 consisting of:

30 -Ar₁
 -O-Ar₁
 -R₉,

- 361 -

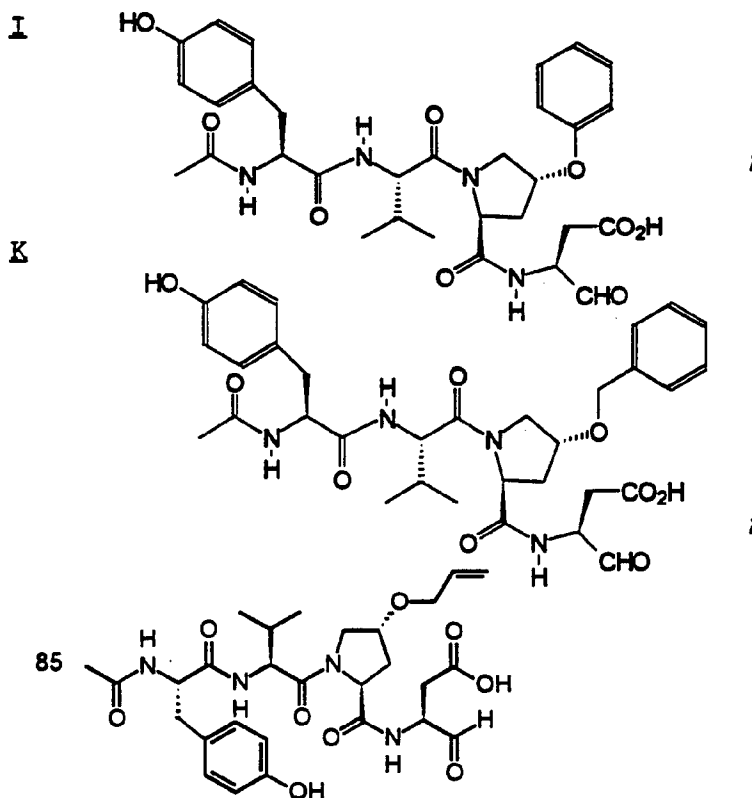
-T₁-R₉, and-(CH₂)_{1,2,3}-T₁-R₉;

each Q₂ is independently selected from the group
 5 consisting of -OH, -NH₂, -CO₂H, -Cl, -F, -Br, -I,
 -NO₂, -CN, -CF₃, and

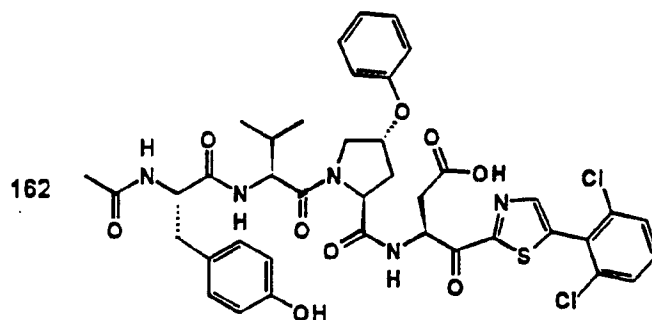
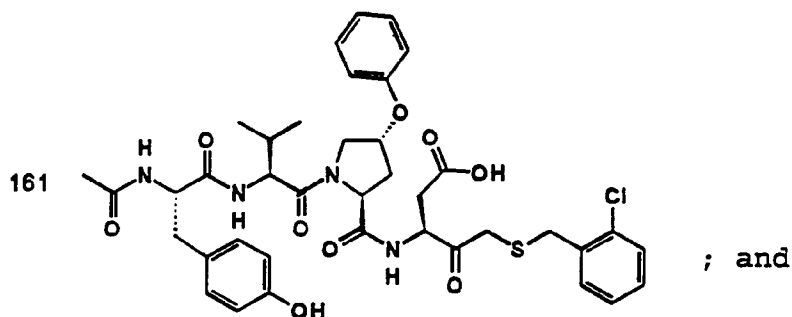
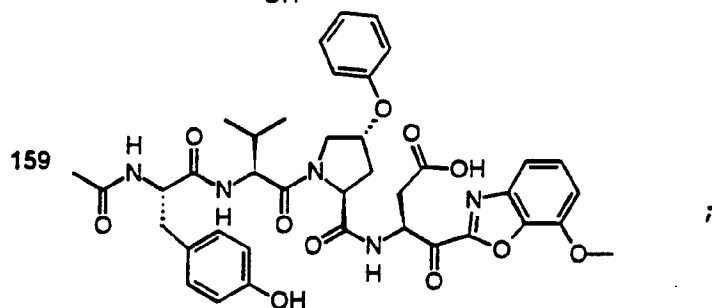
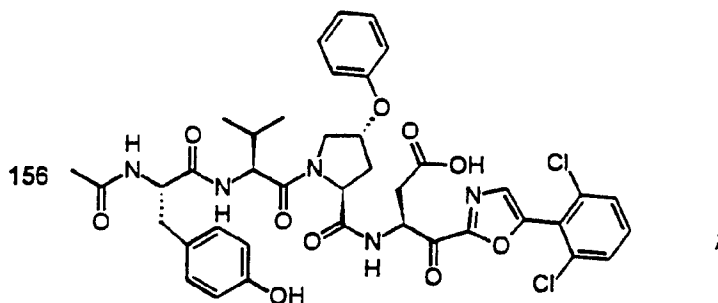


provided that when -Ar₁ is substituted with a Q₁
 group which comprises one or more additional -Ar₁
 groups, said additional -Ar₁ groups are not
 15 substituted with Q₁.

120. The compound according to claim 119,
 selected from the group consisting of:



- 362 -



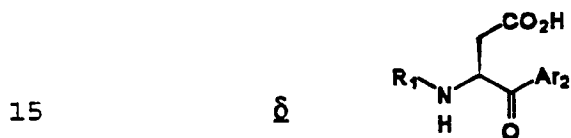
121. The compound according to claim 119,
wherein each A is independently selected from the
group consisting of the α -amino acids:

alanine,
histidine,

- 363 -

lysine,
 phenylalanine,
 proline,
 tyrosine,
 5 valine,
 leucine,
 isoleucine,
 glutamine,
 methionine,
 10 homoproline,
 3-(2-thienyl) alanine, and
 3-(3-thienyl) alanine.

122. A compound represented by the formula:

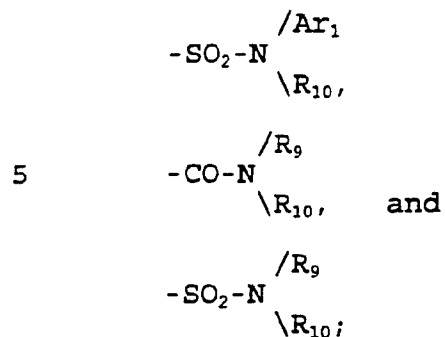


R_1 is $R_5-(A)_p$;

R_5 is selected from the group consisting of:

-H,
 -Ar₁,
 20 -CO-Ar₁,
 -SO₂-Ar₁,
 -R₉,
 -CO-R₉,
 -CO-O-R₉,
 25 -SO₂-R₉,
 -CO-N /Ar₁
 \R₁₀,

- 364 -



10 each A is independently selected from the group consisting of any α -amino acid;

p is 0, 1, 2, 3 or 4;

15 each R₉ is a C₁₋₆ straight or branched alkyl group optionally singly or multiply substituted by -OH, -F, or =O and optionally substituted with one Ar₁ group;


each R₁₀ is independently selected from the group consisting of -H or a C₁₋₆ straight or branched alkyl group;

20 each T₁ is independently selected from the group consisting of:

-CH=CH-,
 -O-,
 -S-,
 -SO-,

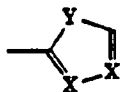
25 each Ar₁ is a cyclic group independently selected from the set consisting of an aryl group which contains 6, 10, 12, or 14 carbon atoms and between 1 and 3 rings, a cycloalkyl group which contains between 3 and 15 carbon atoms and between 1 and 3

- 365 -

rings, said cycloalkyl group being optionally
 benzofused, and a heterocycle group containing
 between 5 and 15 ring atoms and between 1 and 3
 rings, said heterocycle group containing at least one
 5 heteroatom group selected from -O-, -S-, -SO-, -SO₂-,
 =N-, and -NH-, said heterocycle group optionally
 containing one or more double bonds, said heterocycle
 group optionally comprising one or more aromatic
 rings, and said cyclic group optionally being singly
 10 or multiply substituted by -NH₂, -CO₂H,
 -Cl, -F, -Br, -I, -NO₂, -CN, =O, -OH,
 -perfluoro C₁₋₃ alkyl,  CH₂, or -Q₁; and
 15

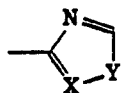
each Ar₂ is independently selected from the
 following group, in which any ring may optionally be
 singly or multiply substituted by -Q₁ and -Q₂:

20 (ii)



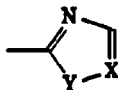
;

(jj)



; and

25 (kk)



;

each Q₁ is independently selected from the group
 consisting of:

30 -Ar₁
 -O-Ar₁
 -R₉,
 -T₁-R₉,

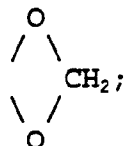
and

- 366 -

$$-(\text{CH}_2)_{1,2,3}-\text{T}_1-\text{R}_9;$$

each Q_2 is independently selected from the group consisting of $-\text{OH}$, $-\text{NH}_2$, $-\text{CO}_2\text{H}$, $-\text{Cl}$, $-\text{F}$, $-\text{Br}$, $-\text{I}$,

5 $-\text{NO}_2$, $-\text{CN}$, $-\text{CF}_3$, and

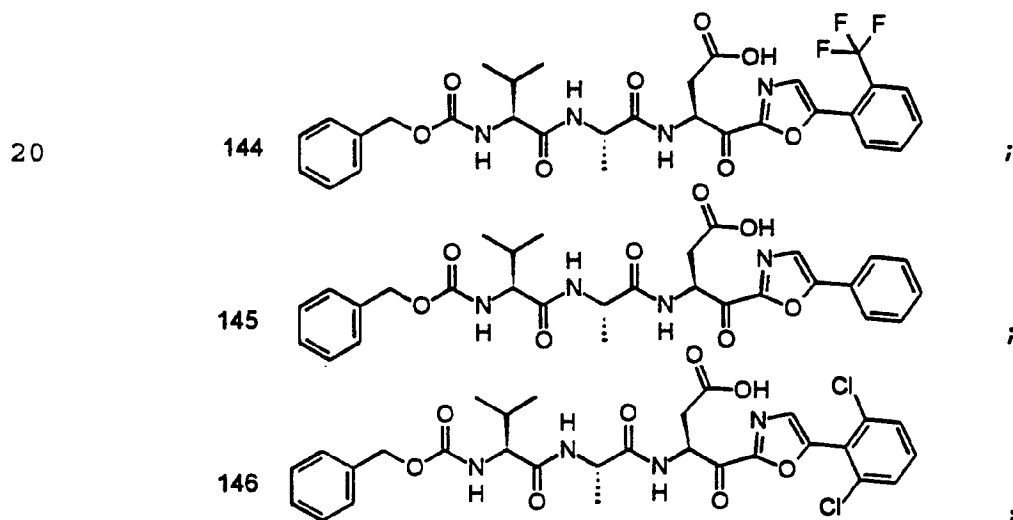


10 provided that when $-\text{Ar}_1$ is substituted with a Q_1 group which comprises one or more additional $-\text{Ar}_1$ groups, said additional $-\text{Ar}_1$ groups are not substituted with Q_1 ;

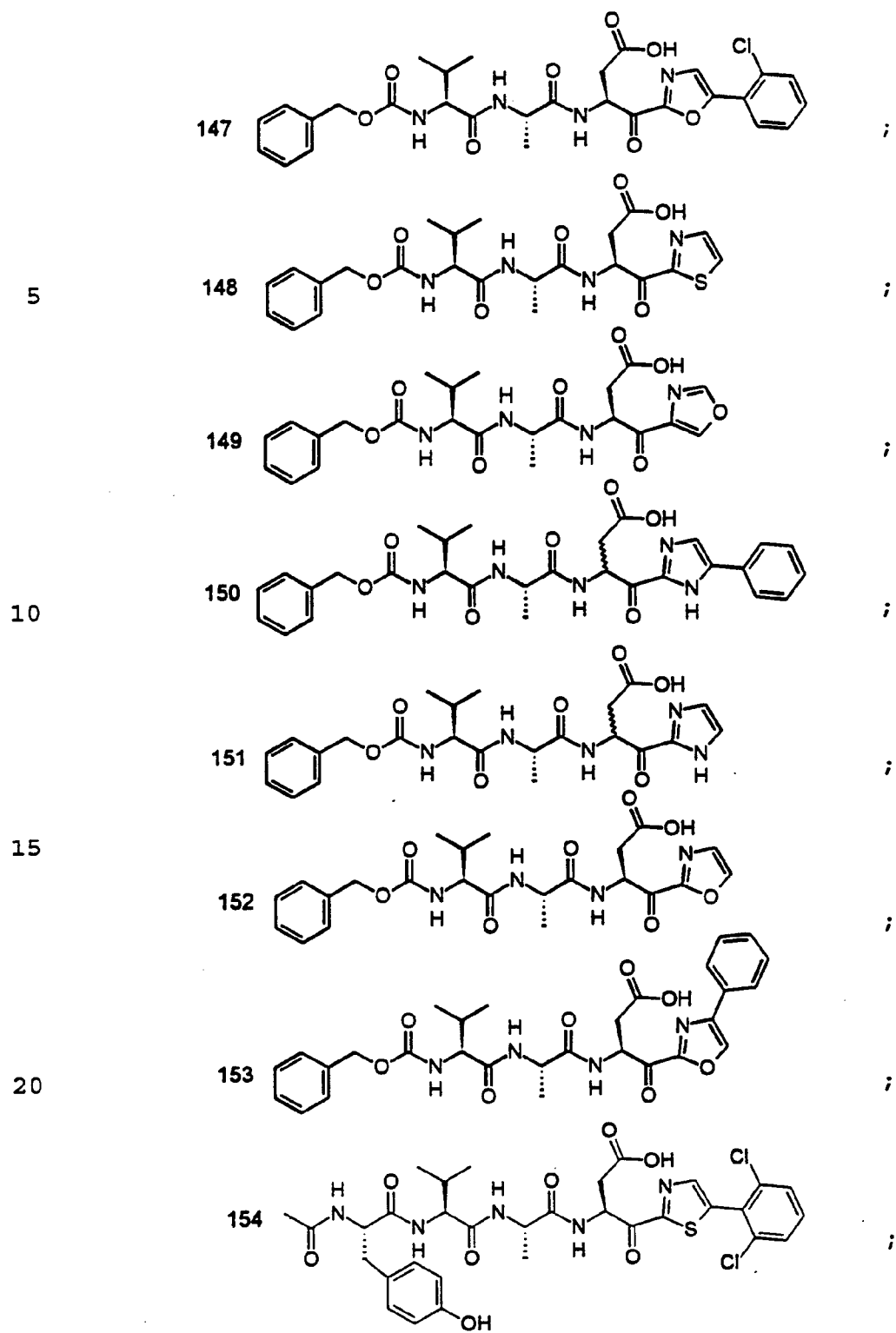
15 each X is independently selected from the group consisting of $=\text{N}-$, and $=\text{CH}-$; and

each Y is independently selected from the group consisting of $-\text{O}-$, $-\text{S}-$, and $-\text{NH}$.

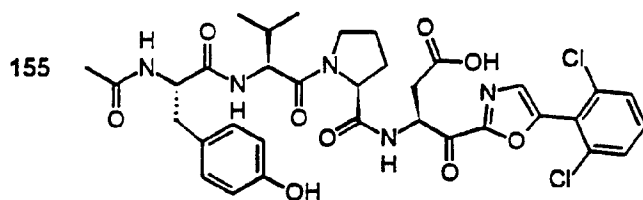
123. The compound according to claim 122, selected from the group consisting of:



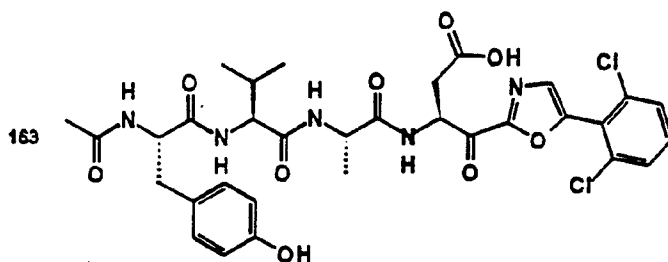
- 367 -



- 368 -



; and



124. The compound according to claim 122,
 5 wherein each A is independently selected from the
 group consisting of the α -amino acids:

alanine,
 histidine,
 lysine,
 10 phenylalanine,
 proline,
 tyrosine,
 valine,
 leucine,
 15 isoleucine,
 glutamine,
 methionine,
 homoproline,
 3-(2-thienyl) alanine, and
 20 3-(3-thienyl) alanine.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 95/07617

A. CLASSIFICATION OF SUBJECT MATTER

IPC 6 C07K5/023 A61K38/06 A61K38/07

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	NATURE (LONDON) (1994), 370(6487), 270-5 CODEN: NATUAS; ISSN: 0028-0836, 28 July 1994 WILSON, KEITH P. ET AL 'Structure and mechanism of interleukin -1.beta. converting enzyme' see page 270, right column, paragraph 2 see page 273, right column, last paragraph - page 274, right column, last paragraph; figures 4,5; table 1 --- -/-	1-18,49, 55, 71-80, 84,90

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search

10 October 1995

Date of mailing of the international search report

16.11.95

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Fuhr, C

INTERNATIONAL SEARCH REPORT

Internat. Application No

PCT/US 95/07617

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	BIOCHEMISTRY, vol. 33, no. 13, 5 April 1994 EASTON, PA US, pages 3934-3940, N.A. THORNBERRY ET AL. 'Inactivation of Interleukin-1beta Converting Enzyme by Peptide (Acyloxy)methyl Ketones' see page 3938, right column, last paragraph - page 3940, left column, paragraph 3; tables 1,2 ---	1-18,49, 55, 71-80, 84,90, 105,107
X	JOURNAL OF MEDICINAL CHEMISTRY, vol. 37, no. 5, 4 March 1994 WASHINGTON US, pages 563-564, R.E. DOLL ET AL. 'P1 Aspartate-Based Peptide alpha-((2,6-Dichlorobenzoyl)oxy)methyl Ketones as Potent Time-Dependent Inhibitors of Interleukin-1beta-Converting Enzyme' see scheme 1 see table 1 ---	1-18,49, 55, 71-80, 84,90, 105,107
X	EP,A,0 519 748 (MERCK & CO INC) 23 December 1992 see claims; examples ---	1-18,49, 55, 71-80, 84,90, 105,107
X	WO,A,93 09135 (SANDOZ AG ;SANDOZ AG (DE); SANDOZ LTD (CH)) 13 May 1993 see claims; examples ---	1-18,23, 26, 47-49, 71-80, 84,105, 107,119
X	WO,A,93 14777 (MERCK & CO INC) 5 August 1993 see claims; examples ---	1-18,49, 55, 71-80, 84,90, 105,107
X	WO,A,93 16710 (MERCK & CO INC) 2 September 1993 see claims; examples ---	1-18,49, 55, 71-80, 84,90, 105,107

-/--

INTERNATIONAL SEARCH REPORT

Intern. Application No

PCT/US 95/07617

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 529 713 (MERCK & CO INC) 3 March 1993 see claims; examples ---	1-18,49, 55, 71-80, 84,90, 105,107
X	EP,A,0 533 350 (MERCK & CO INC) 24 March 1993 see claims; examples ---	1-18,49, 55, 71-80, 84,90, 105,107
X	EP,A,0 547 699 (MERCK & CO INC) 23 June 1993 see claims; examples ---	1-18,49, 55, 71-80, 84,90
X	BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 4, no. 19, 1994 pages 2359-2364, M.D. MULLICAN ET AL. 'The Synthesis and Evaluation of Peptidyl Aspartyl Aldehydes as Inhibitors of ICE' see page 2363, paragraph 2 - paragraph 3; table ---	1-18,49, 55, 71-80, 84,90
P,X	WO,A,95 05192 (MERCK & CO INC ;HAGMANN WILLIAM K (US); MJALLI ADNAN M (US); ZHAO) 23 February 1995 see claims; examples ---	1-18,49, 55, 71-80, 84,90
P,X	EP,A,0 644 197 (STERLING WINTHROP INC) 22 March 1995 see claims; examples ---	1-18
P,X	EP,A,0 644 198 (STERLING WINTHROP INC) 22 March 1995 see claims; examples -----	1-18

INTERNATIONAL SEARCH REPORT

1. International application No.

PCT/US 95/ 07617

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Please see annex!
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/210

Claims searched completely: 102-109, 111-113, 115-118, 120-124
Claims searched incompletely: 1-101, 110, 114, 119

In view of the large number of compounds falling under claims 1-101, 110, 114, 119, and of the absence of any sensible support for these claims in the description, the Search Division considers that it is not economically reasonable to draw a search report covering the entire subject matter of claims 1-101, 110, 114, 119. The search for the claims 1-101, 110, 114, 119 has therefore been limited and includes all the real examples given in the description and covers all similar compounds having the alleged activities as well (see also remark)

Remark: As far as the claim 76 is directed to a method of treatment of the human and/or animal body, the search has been carried out on the alleged effects of the compound and/or composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/07617

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0519748	23-12-92	CA-A- 2071674	22-12-92
		JP-A- 5255218	05-10-93
		JP-B- 6102642	14-12-94
		US-A- 5434248	18-07-95

WO-A-9309135	13-05-93	AU-A- 2885292	07-06-93
		CA-A- 2116653	13-05-93
		CZ-A- 9401067	15-12-94
		EP-A- 0611375	24-08-94
		FI-A- 942061	04-05-94
		HU-A- 68200	29-05-95
		JP-T- 7500828	26-01-95
		NO-A- 941629	04-07-94
		NZ-A- 244985	27-06-95
		PT-A- 101027	28-02-94

WO-A-9314777	05-08-93	AU-B- 3479593	01-09-93

WO-A-9316710	02-09-93	AU-B- 3666893	13-09-93
		CA-A- 2129976	02-09-93
		EP-A- 0627926	14-12-94
		JP-T- 7504194	11-05-95
		US-A- 5430128	04-07-95

EP-A-0529713	03-03-93	US-A- 5278061	11-01-94
		JP-A- 5252950	05-10-93

EP-A-0533350	24-03-93	CA-A- 2076159	17-02-93
		JP-A- 5227961	07-09-93

EP-A-0547699	23-06-93	CA-A- 2085300	20-06-93
		JP-A- 5271274	19-10-93
		JP-B- 7017676	01-03-95

WO-A-9505192	23-02-95	AU-B- 7714594	14-03-95

EP-A-0644197	22-03-95	AU-B- 6451494	08-12-94
		CZ-A- 9401379	14-06-95
		FI-A- 942625	05-12-94
		JP-A- 7025887	27-01-95

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 95/07617

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP-A-0644197		NO-A- 942065	05-12-94
<hr/>			
EP-A-0644198	22-03-95	AU-B- 6347394	27-04-95
		CZ-A- 9401355	15-12-94
		FI-A- 942624	04-12-94
		HU-A- 68689	28-07-95
		JP-A- 7089951	04-04-95
		NO-A- 942064	05-12-94
<hr/>			